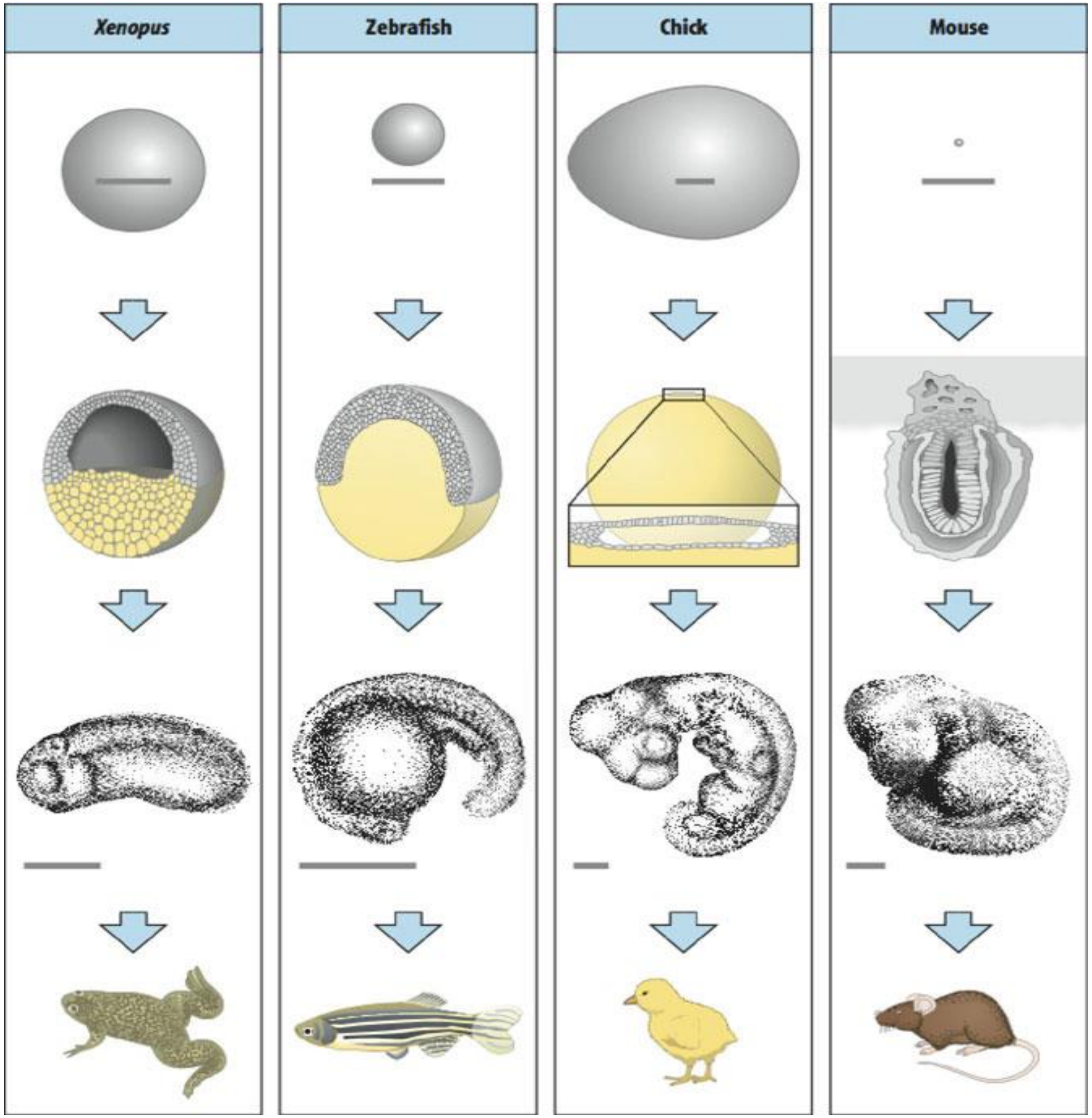
Introduction to cell fate and plasticity during embryonic development

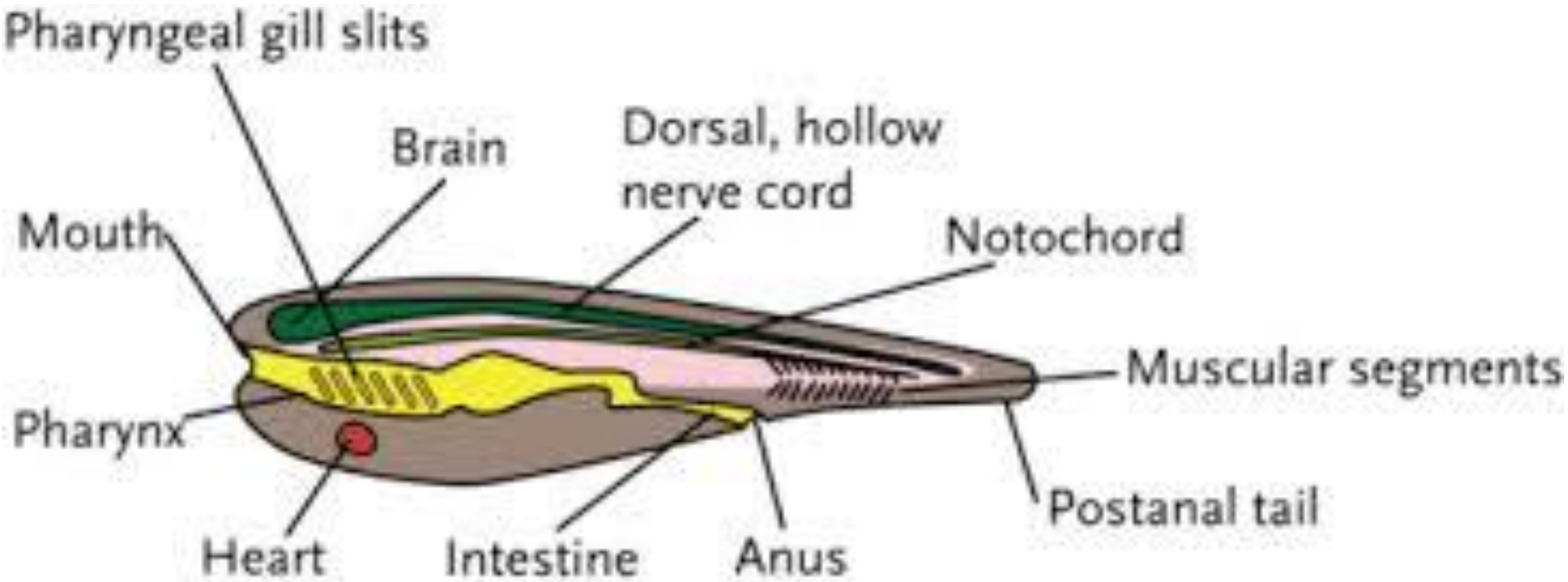
Francois Fagotto, CRBM, U. Montpellier and CNRS

Introduction, fate maps, definitions
Cell determination = multistep process (ex: muscle)
Induction
Morphogens (ex: BMP)
Combinatorial control
Competence
Lateral inhibition
Asymmetric division/asymmetric distribution (germ cells)

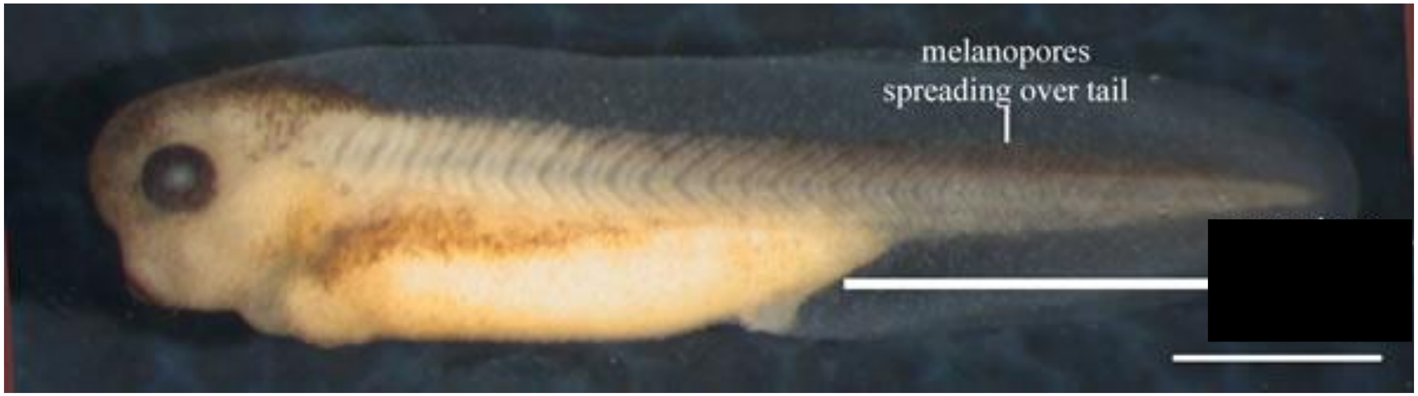
Introduction Vertebrate embryos: different eggs, different gastrulation, but similar general organization of the "larval" stage)

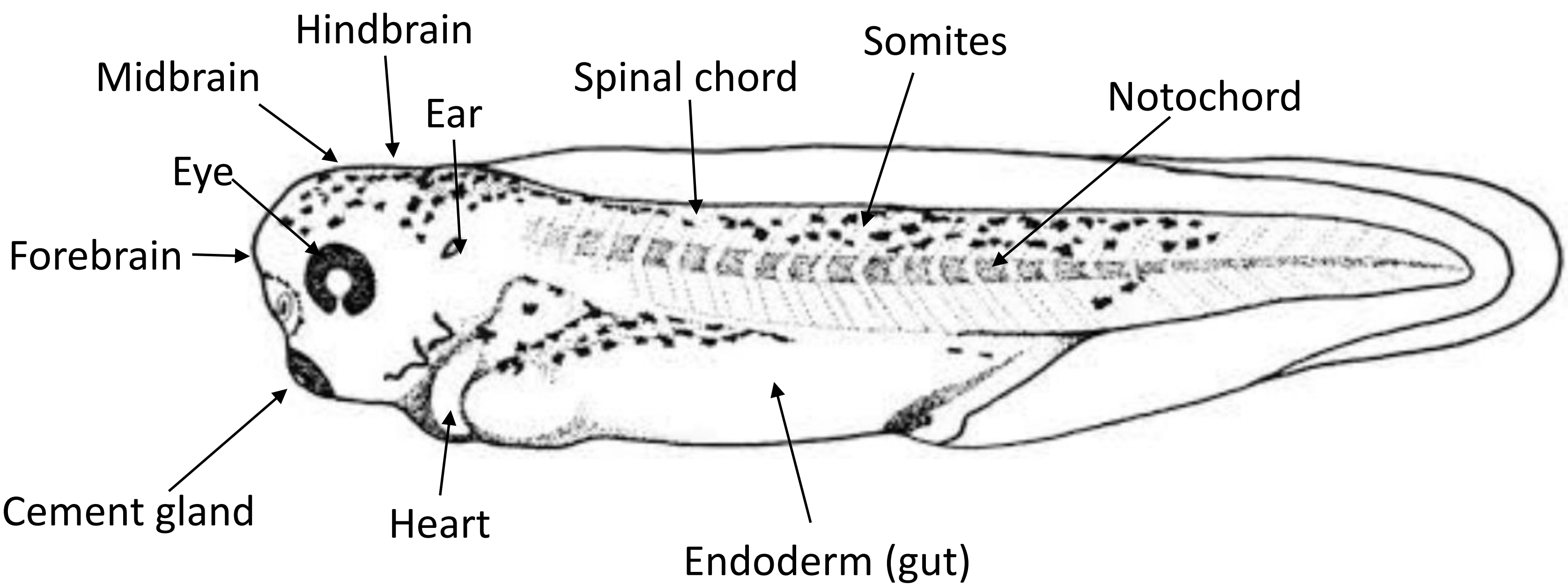


The basic "chordate" body plan



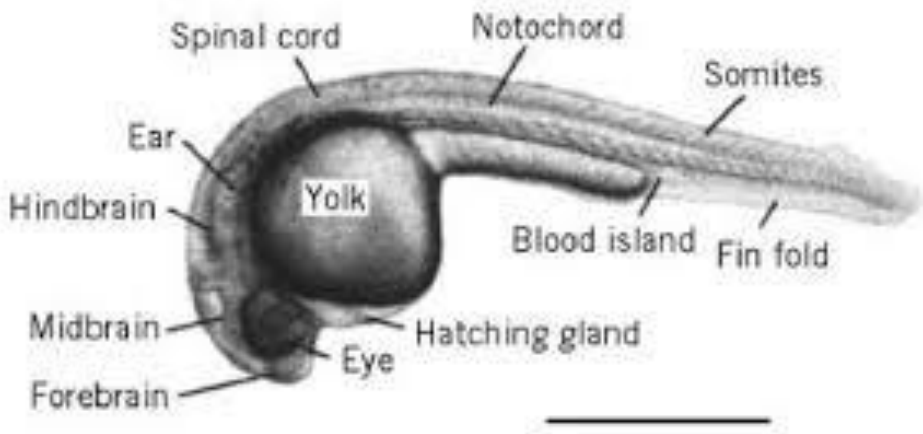
Xenopus early tadpole: prototypic vertebrate organization



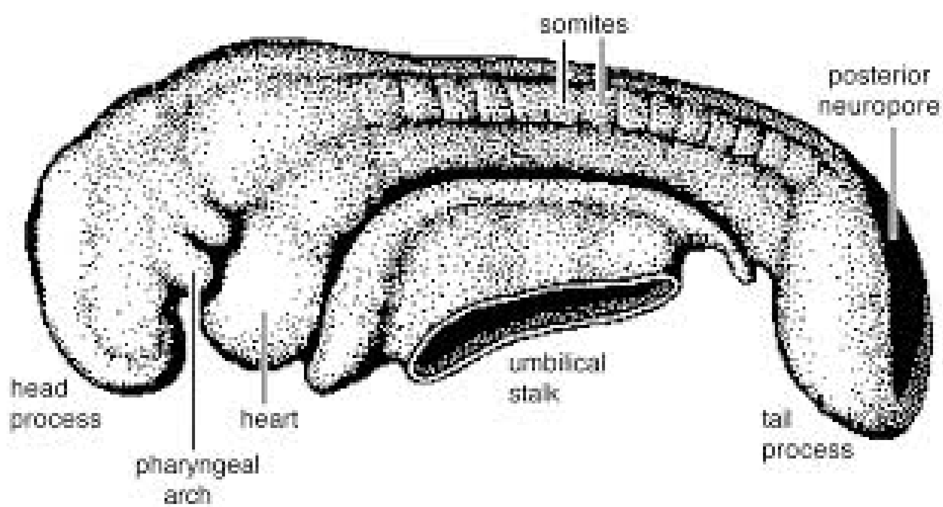


“Larval” stage: Conserved general vertebrate organization

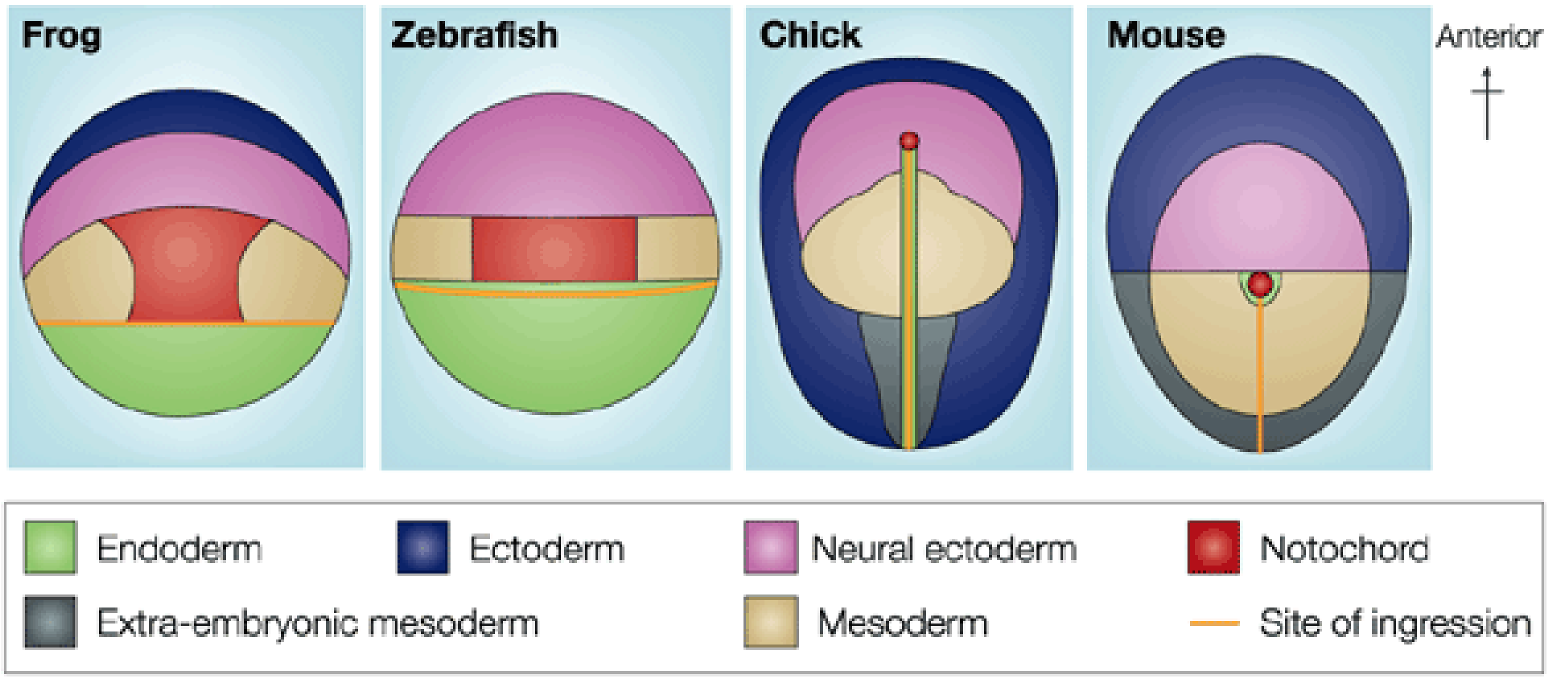
Fish



Mouse

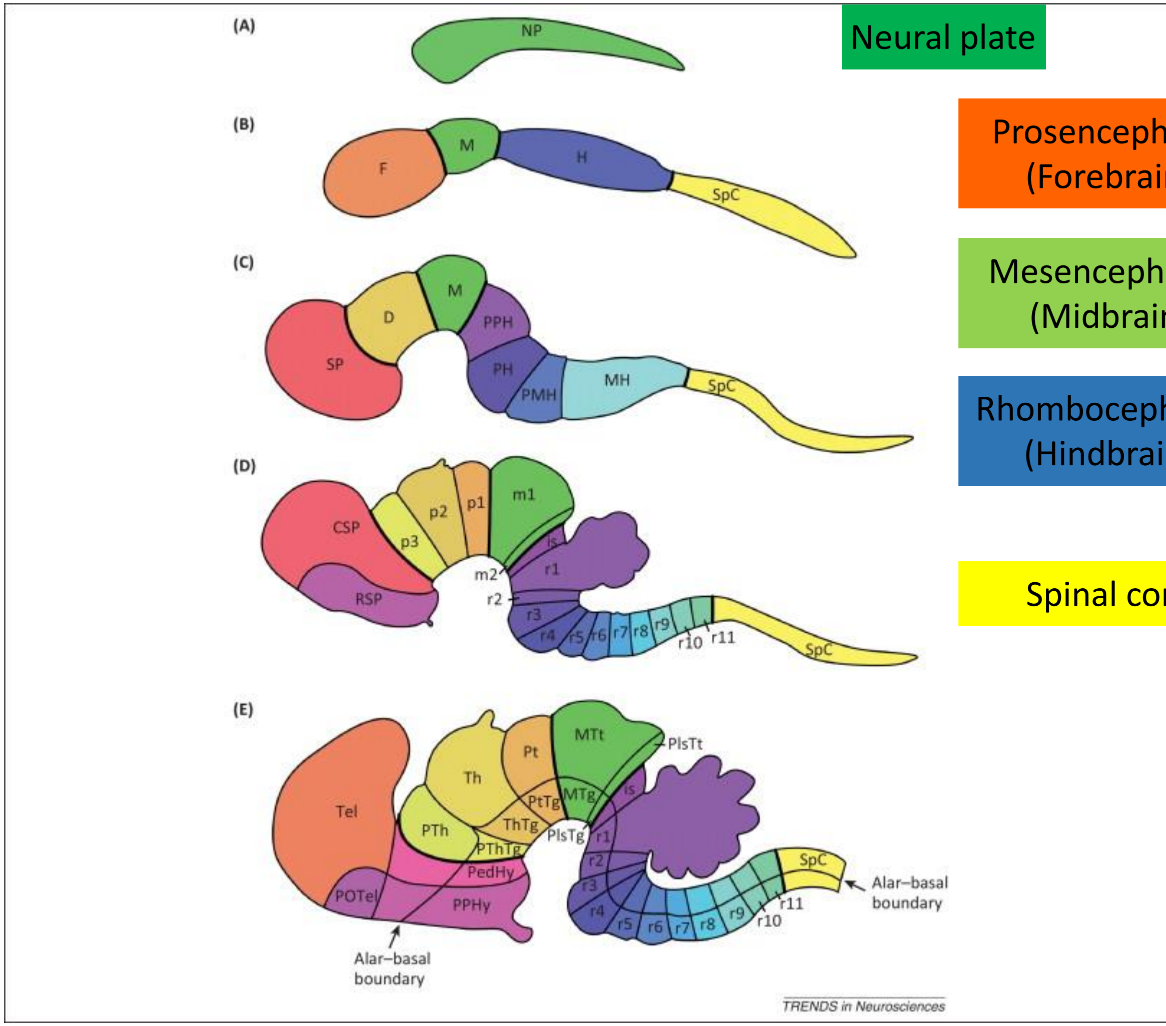


Vertebrate embryos: Diverse topography for conserved organization



Nature Reviews | Neuroscience

Neuroderm: Conserved basic structure and evolution



Neural plate

Prosencephalon (Forebrain)

Telencephalon (cerebrum = cortex)

Diencephalon (eyes, hypothalamus,…)

Mesencephalon (Midbrain)

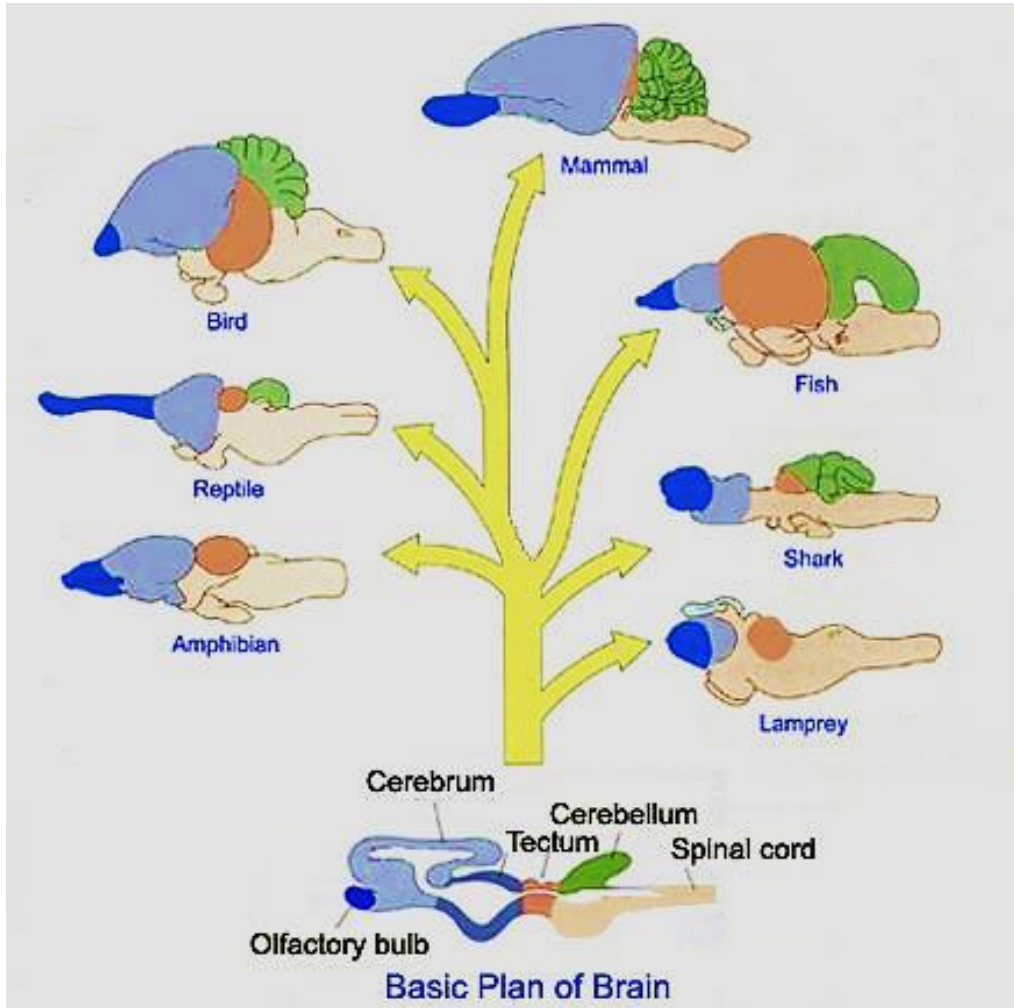
Rhombocephalon (Hindbrain)

Metencephalon (cerebellum)

Myelencephanlon (medulla oblunga)

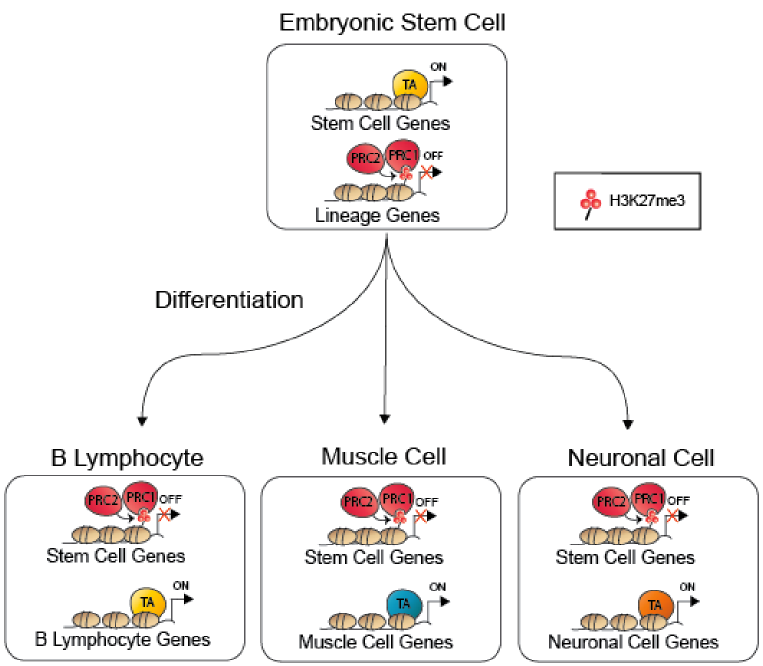
Spinal cord

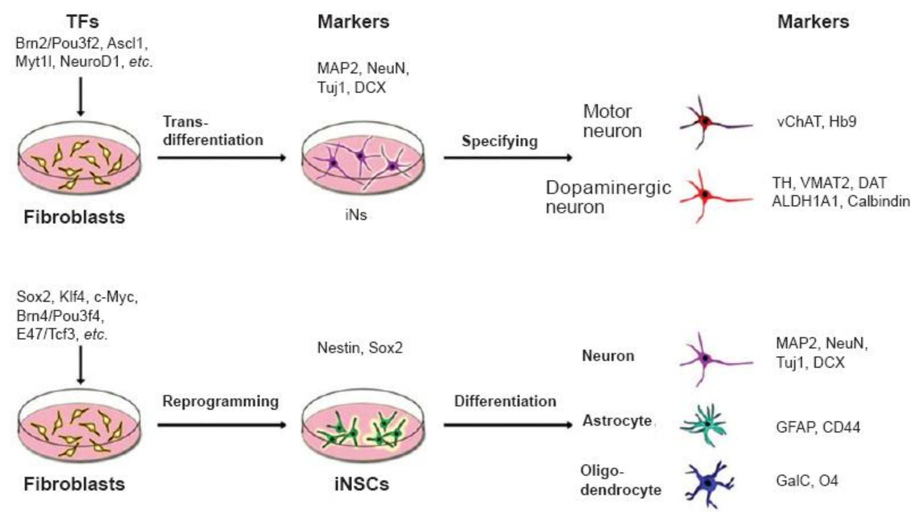
“Larval” stage: Conserved organization of the neuroderm/brain



Introduction

<u>In vitro</u>: 1) embryonic stem cells can be forced to differentiate into ANY cell type
2) Differentiated cells can be de-differentiated and produce other cell types

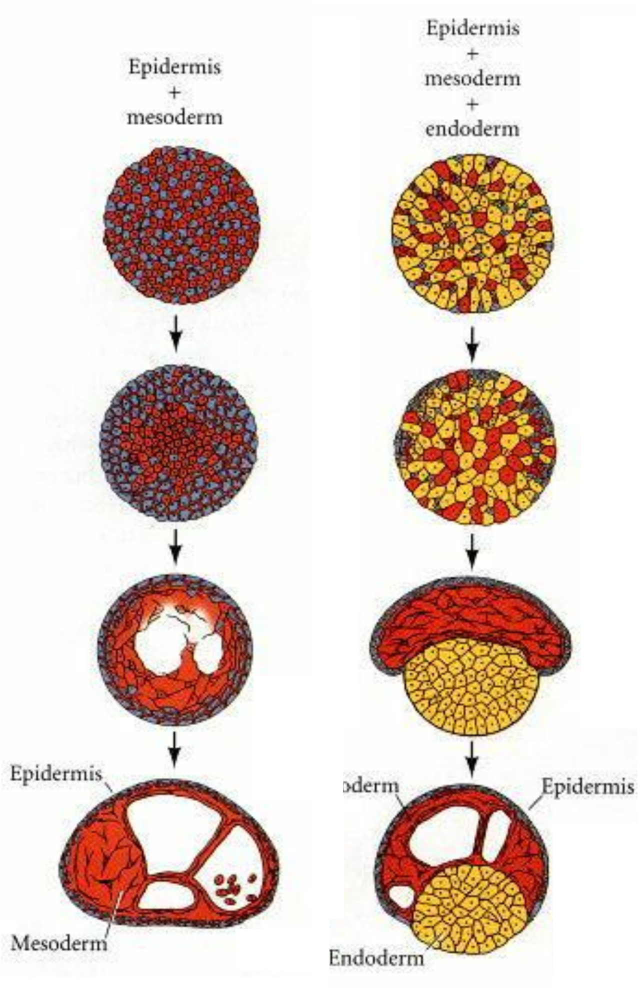




!! Getting new tissues/organs !!
!! Any issue at stake??

Introduction

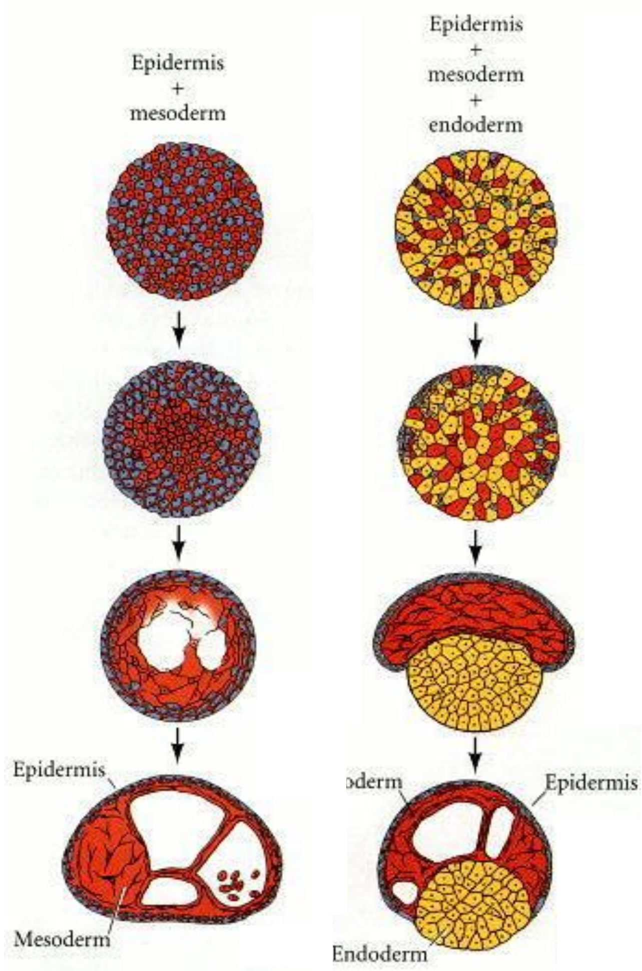
Partial self-organization capacities

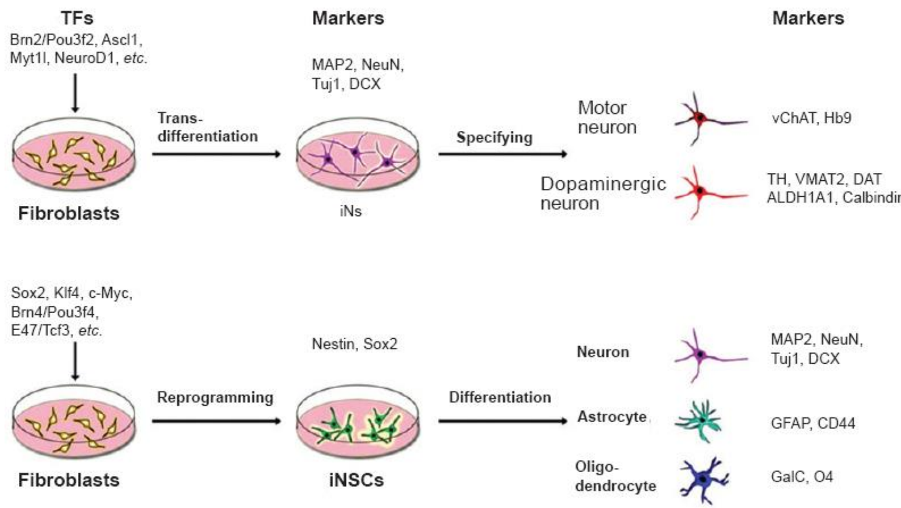


J. Holtfreter, 1930-39, Townes and Holtfreter (1955)

Introduction

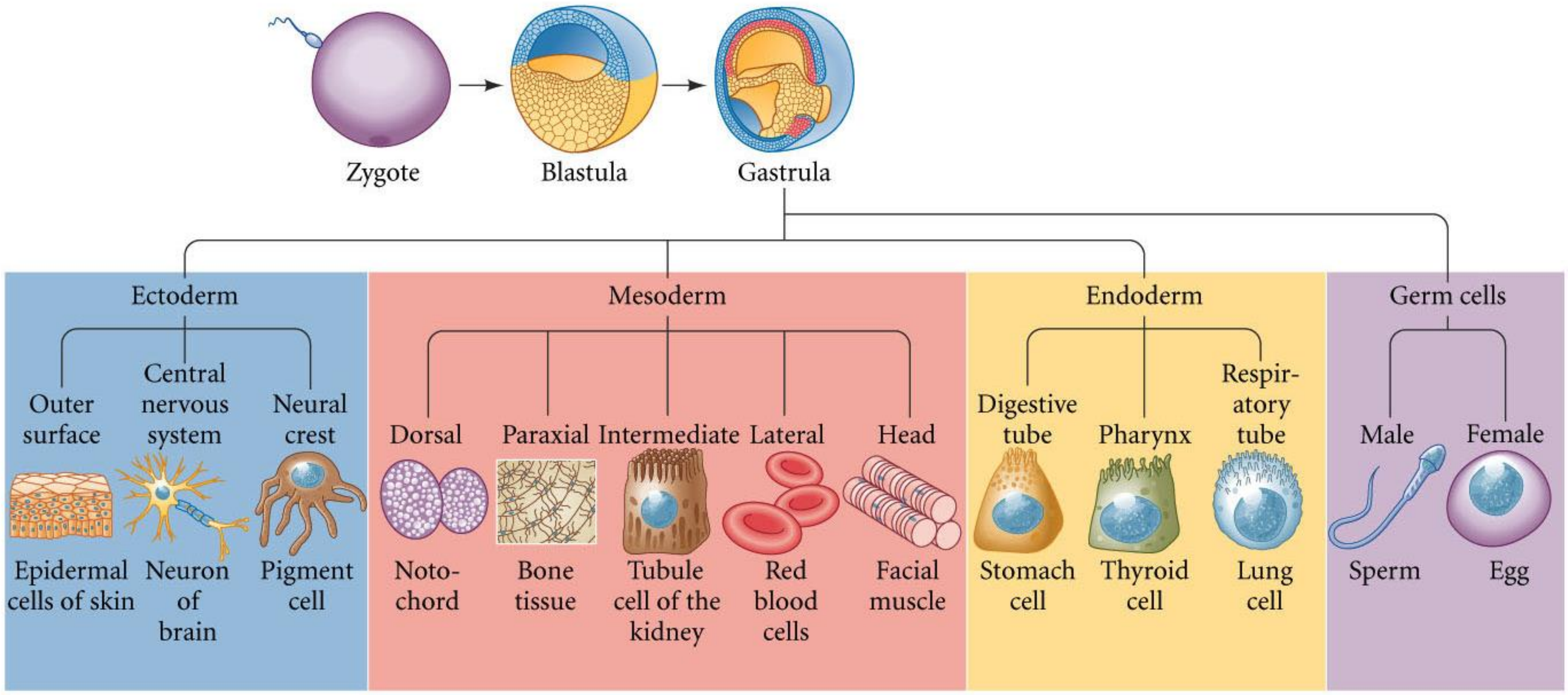
But this does not make a viable organism (not even organs!!)





Introduction

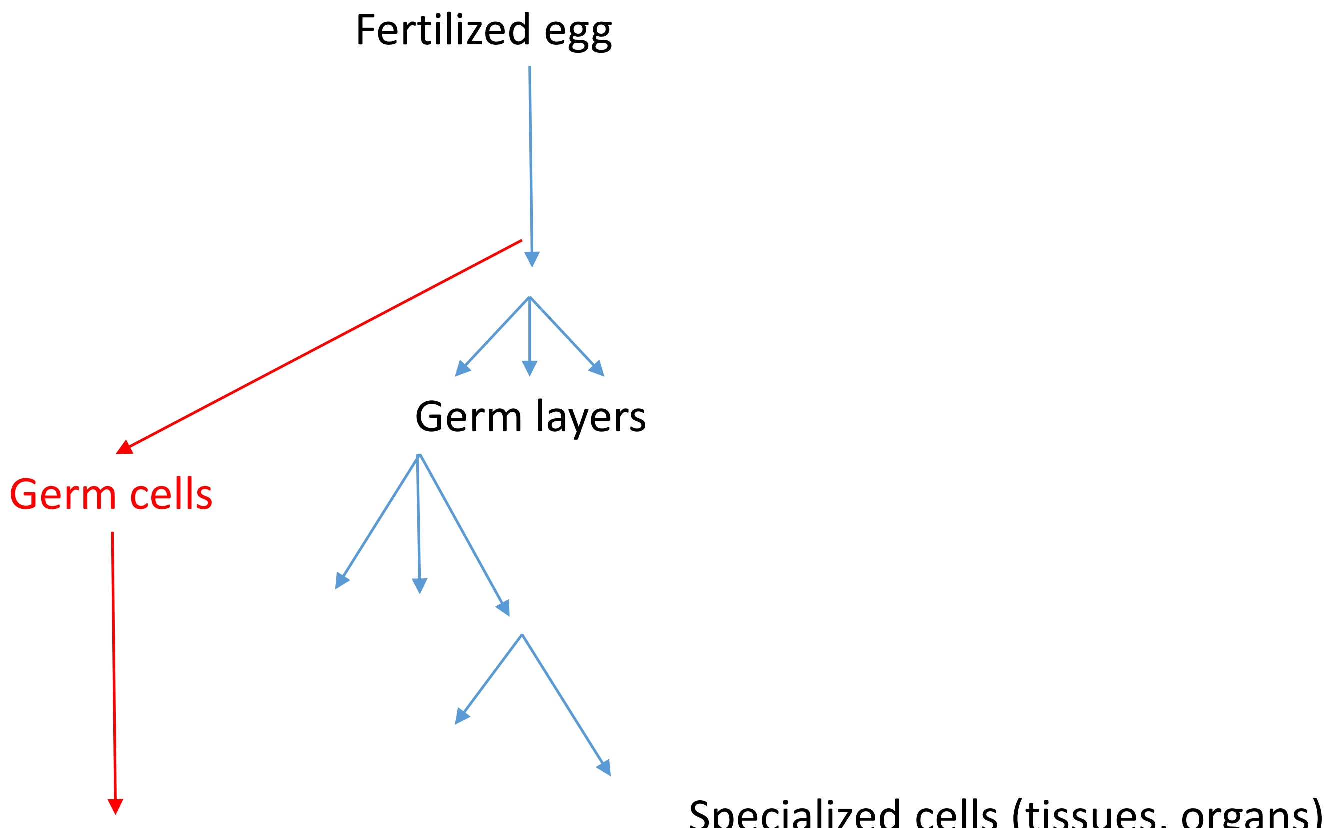
Embryonic development: from egg to organism



DEVELOPMENTAL BIOLOGY, Eighth Edition, Figure 1.1

Definitions

Cell fate determination



Definitions

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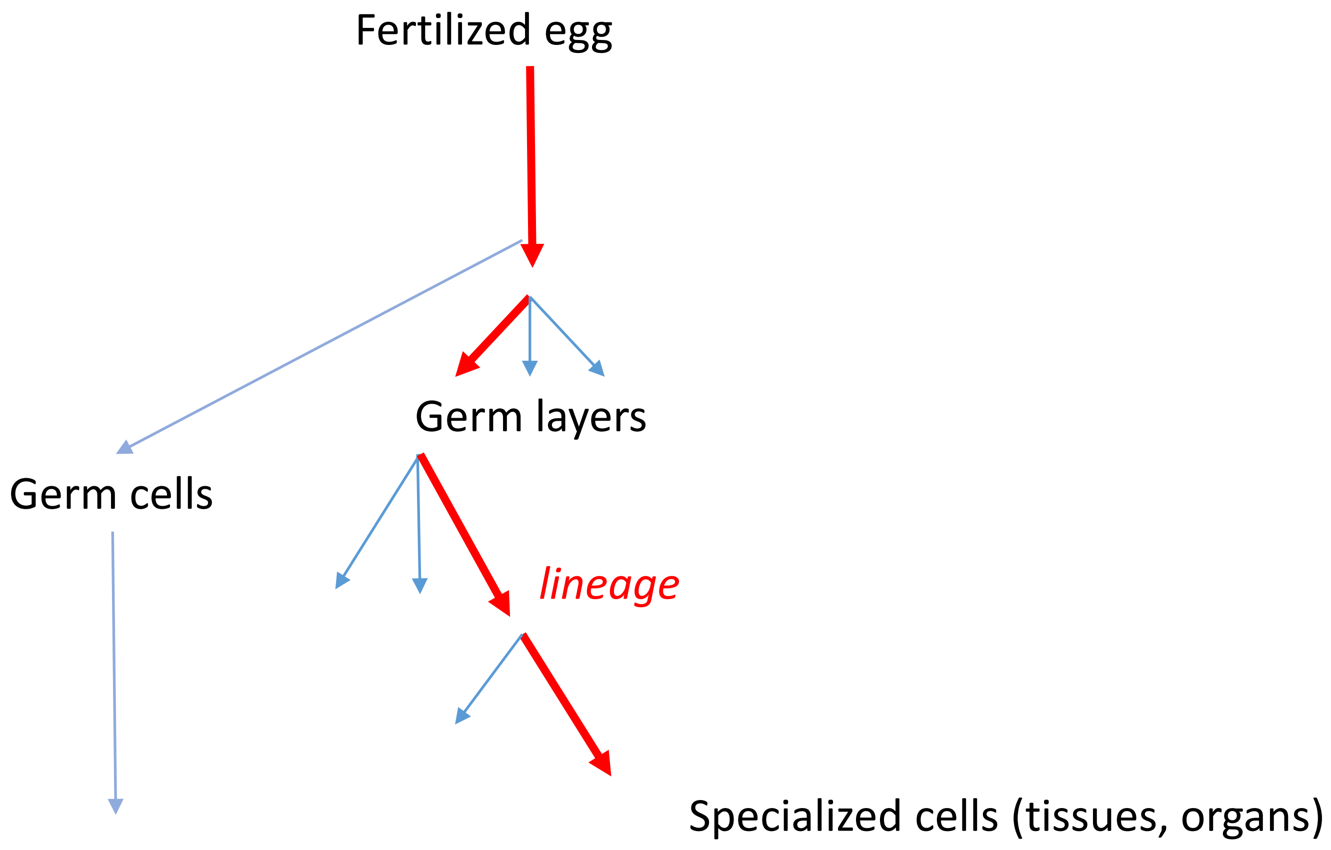
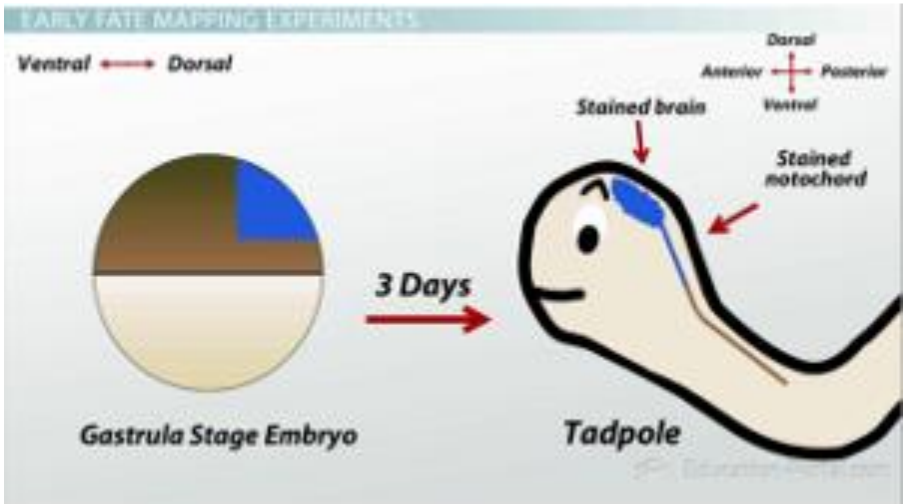


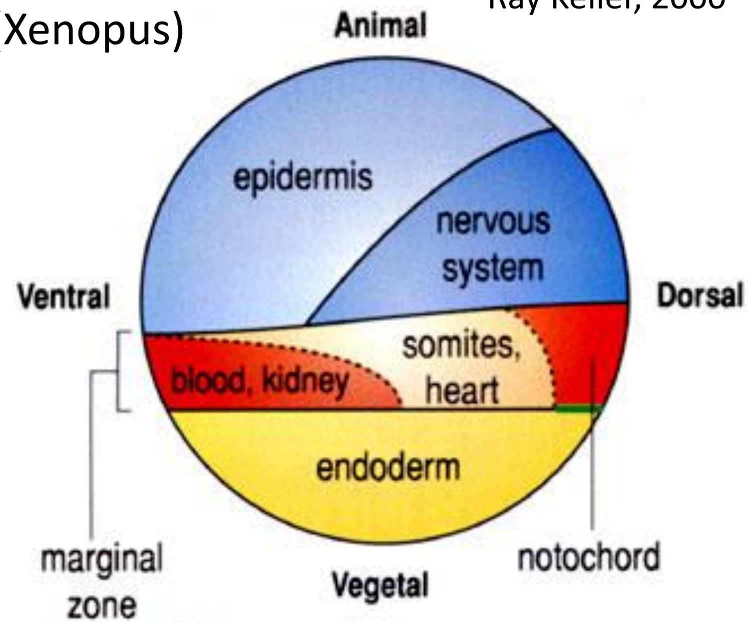
Fate mapping – following differentiation

Amphibians (Xenopus)

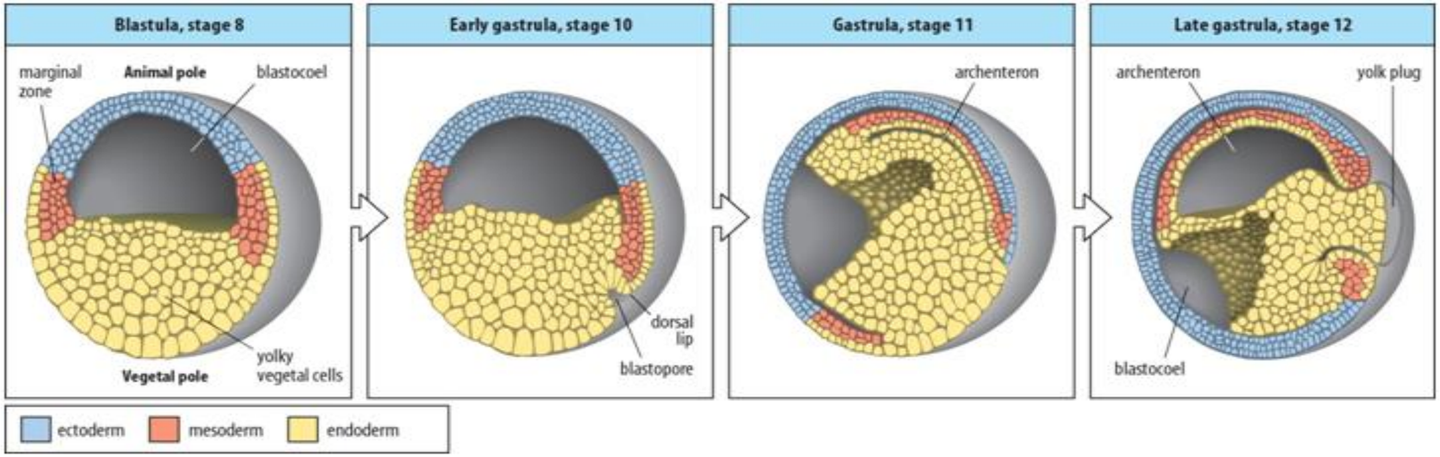


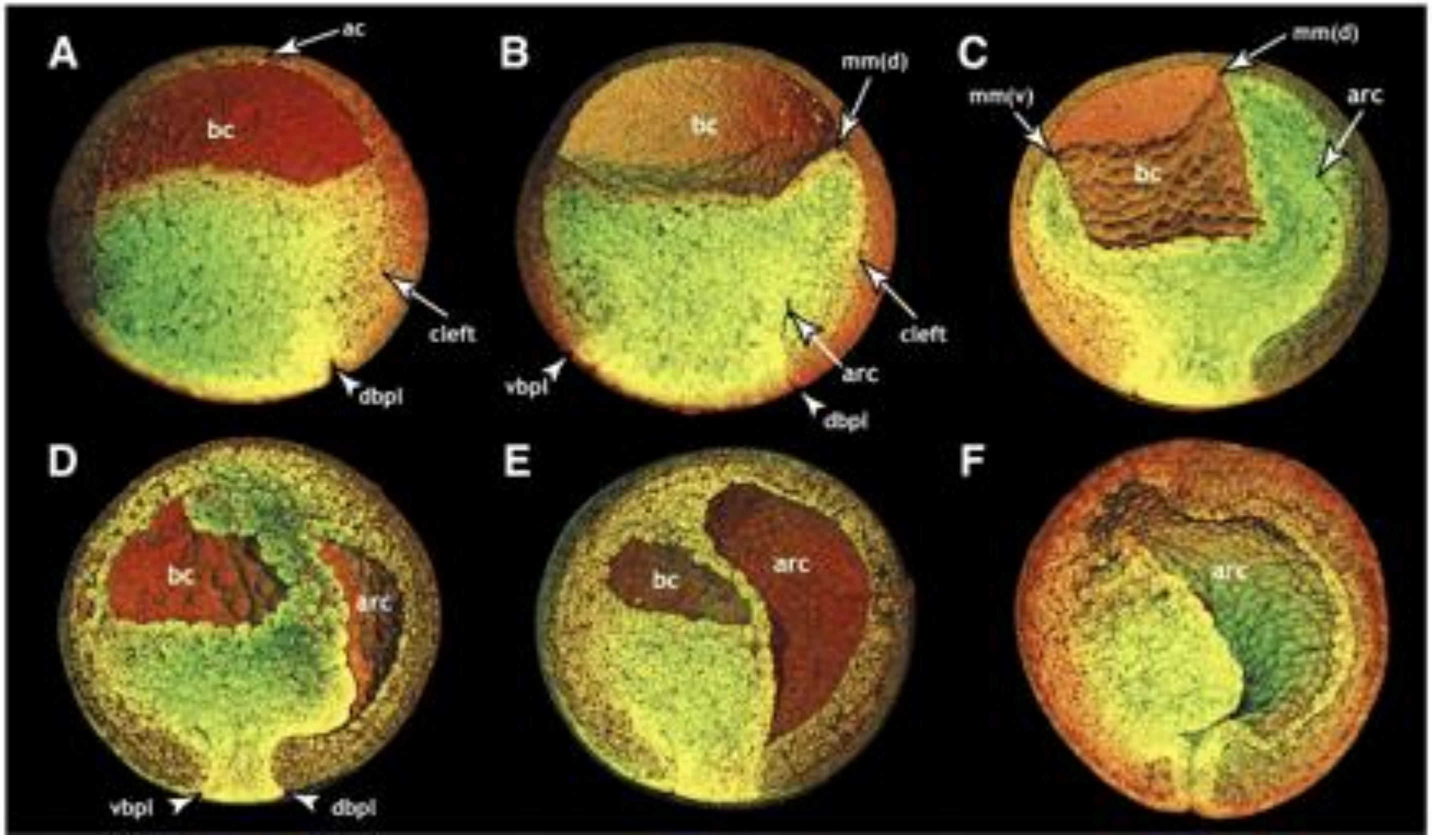
Walter Vogt, 1925

Ray Keller, 2000



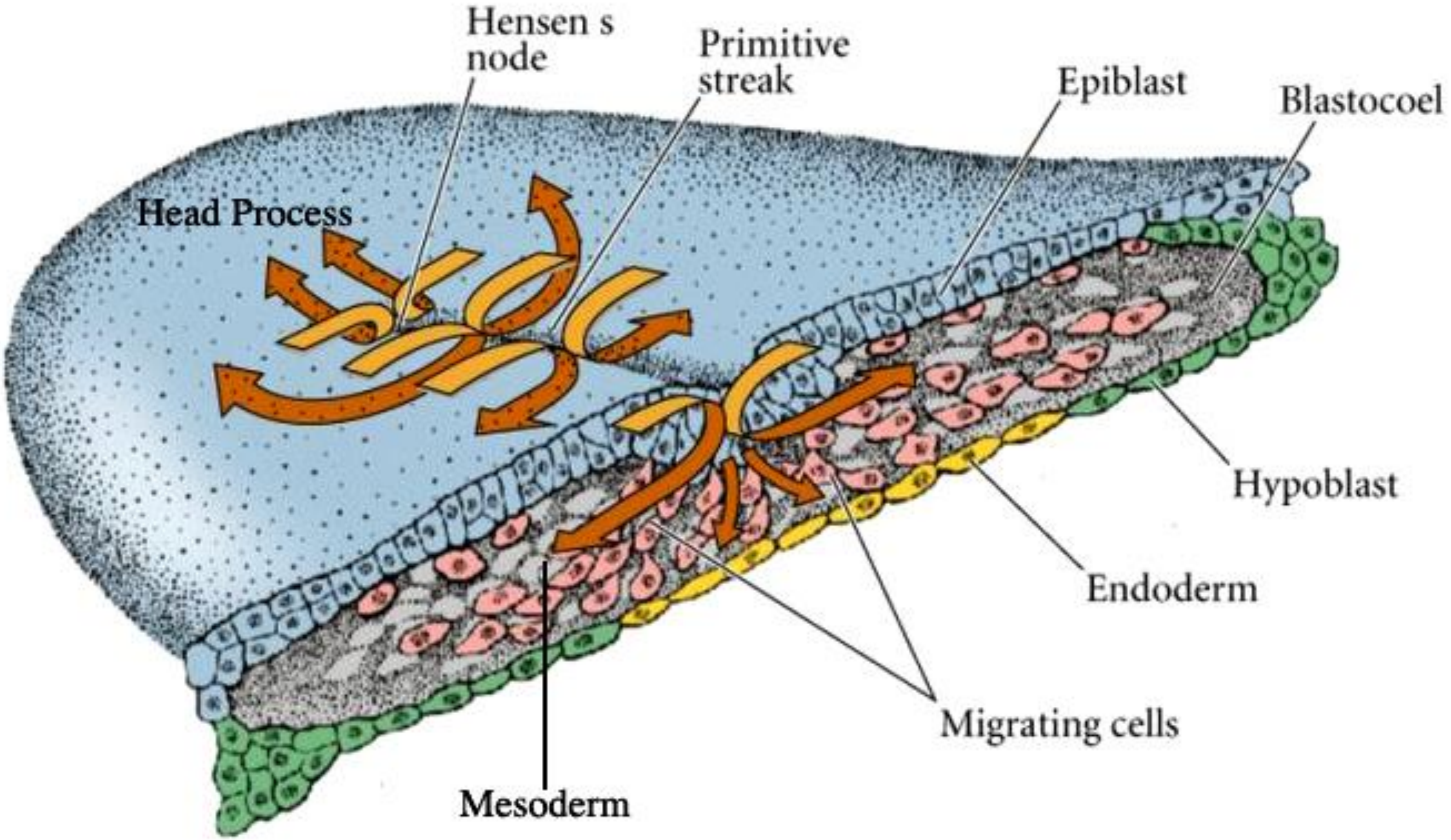
Fate mapping





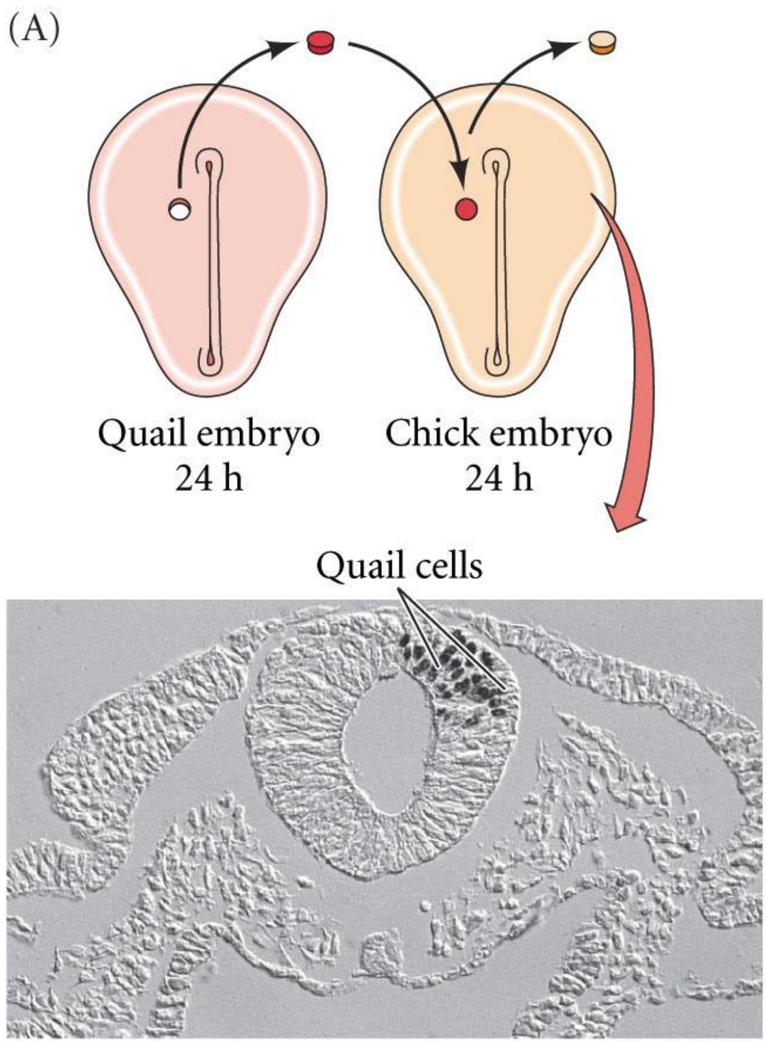
Fate mapping

Gastrulation in chick embryo

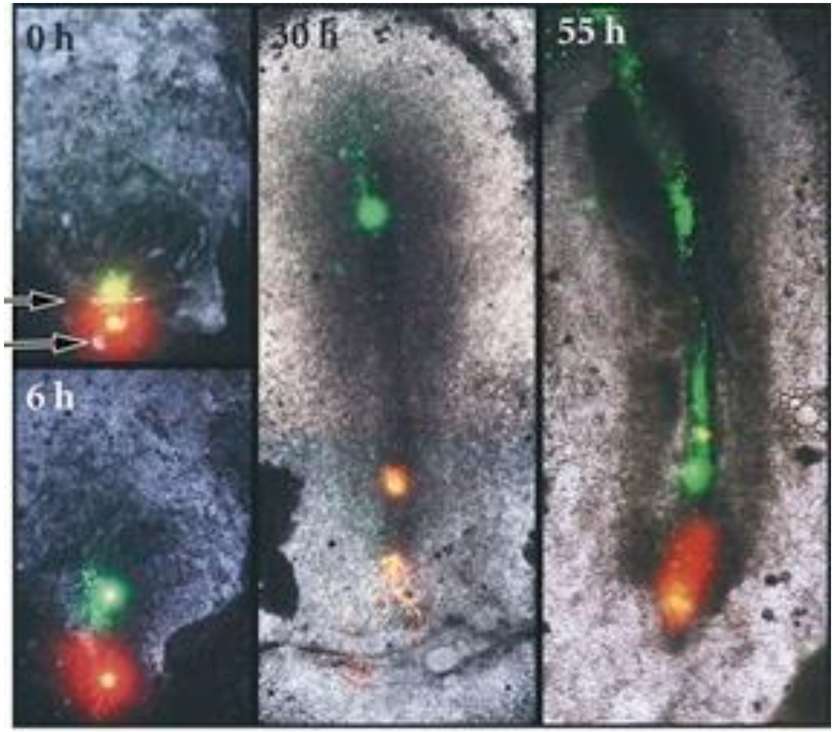


Fate mapping

Gastrulation in chick embryo

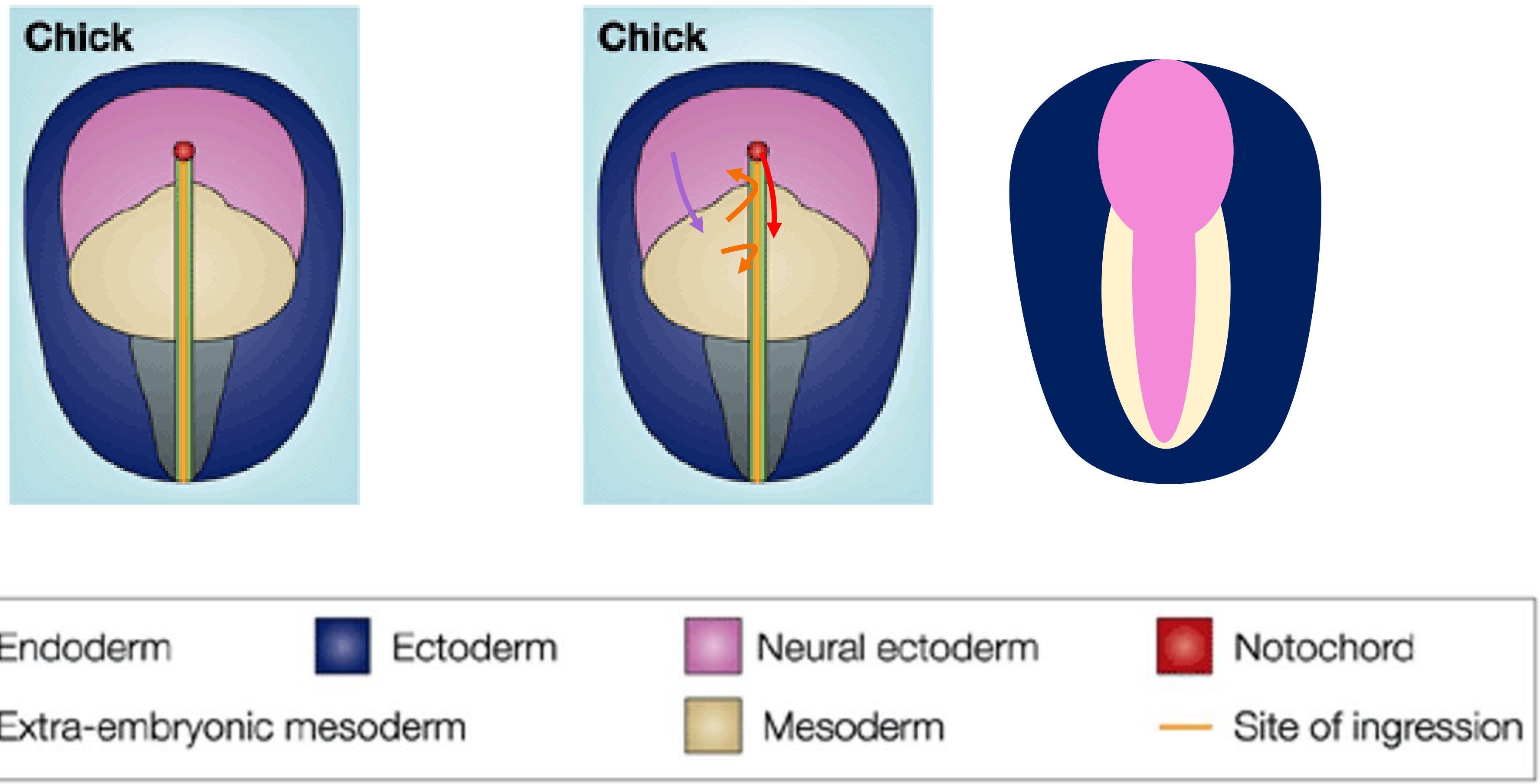


Chick embryo with region of quail cells on the neural tube



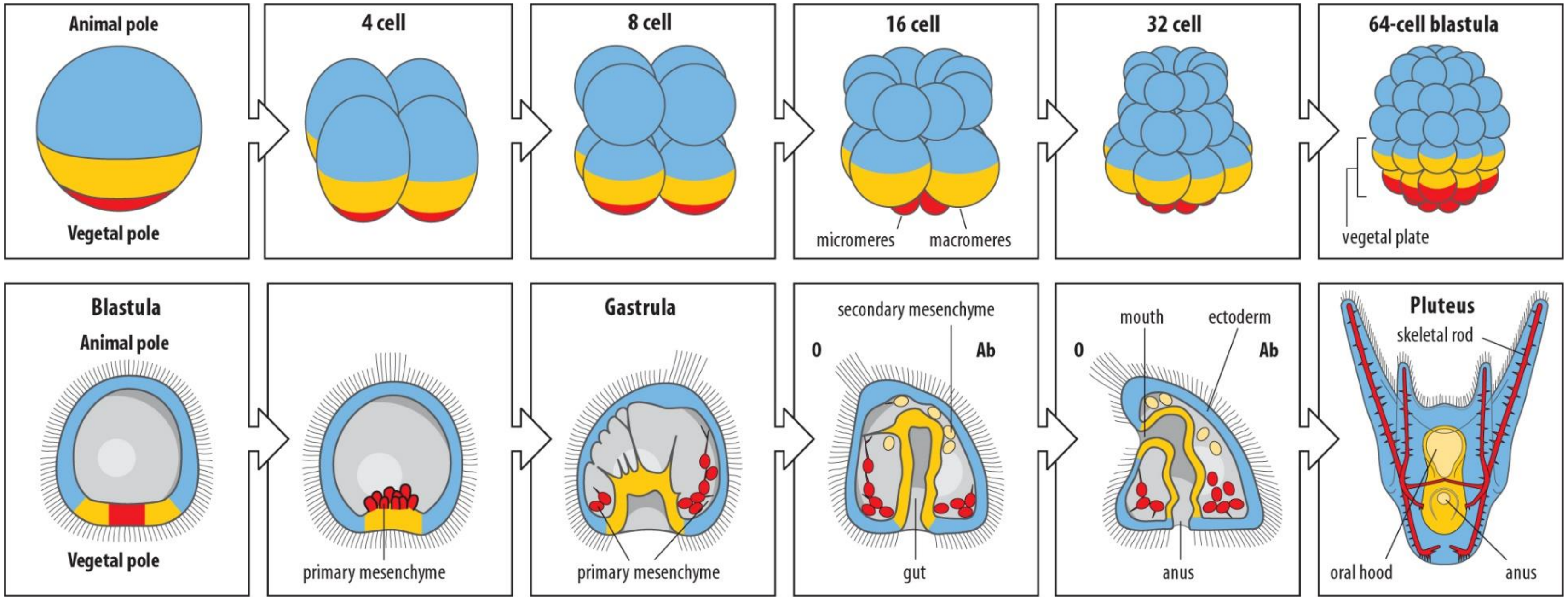
Fate mapping

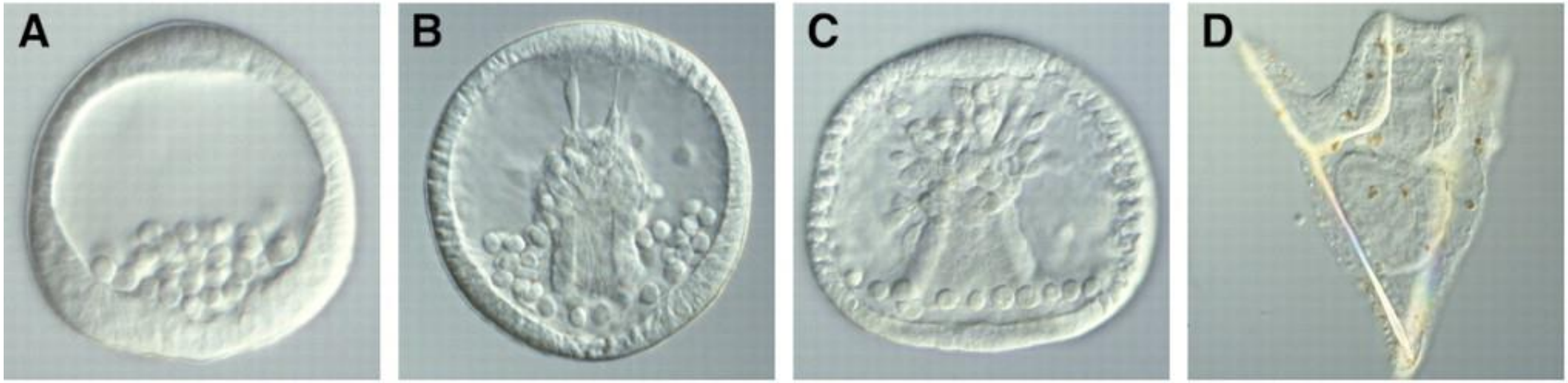
Gastrulation in chick embryo



Fate mapping

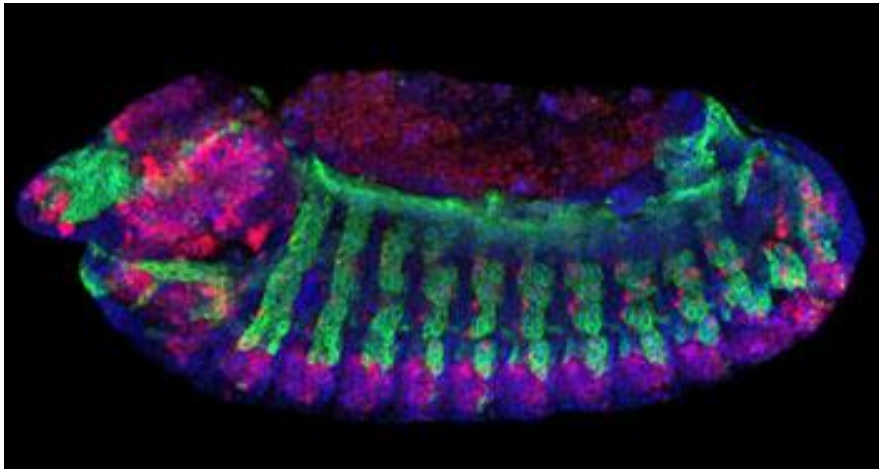
Sea urchin

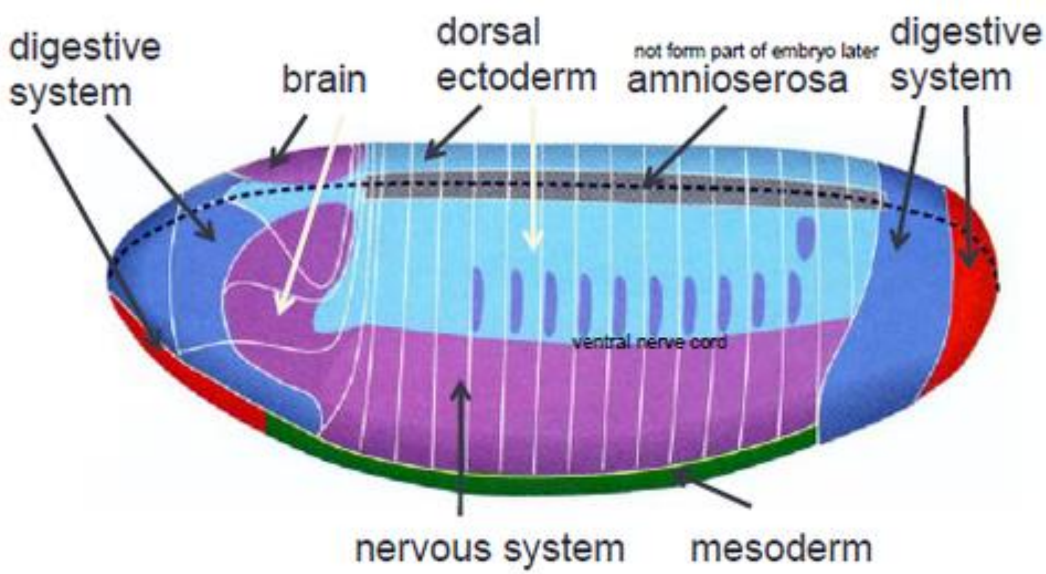


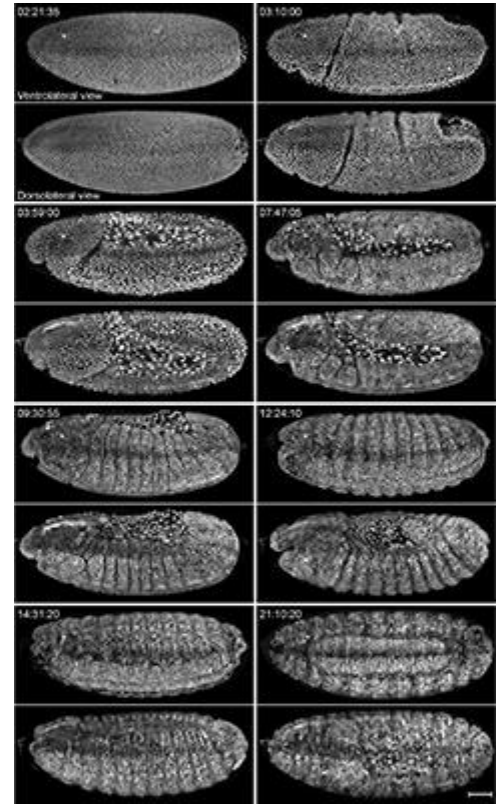


Fate mapping

Drosophila



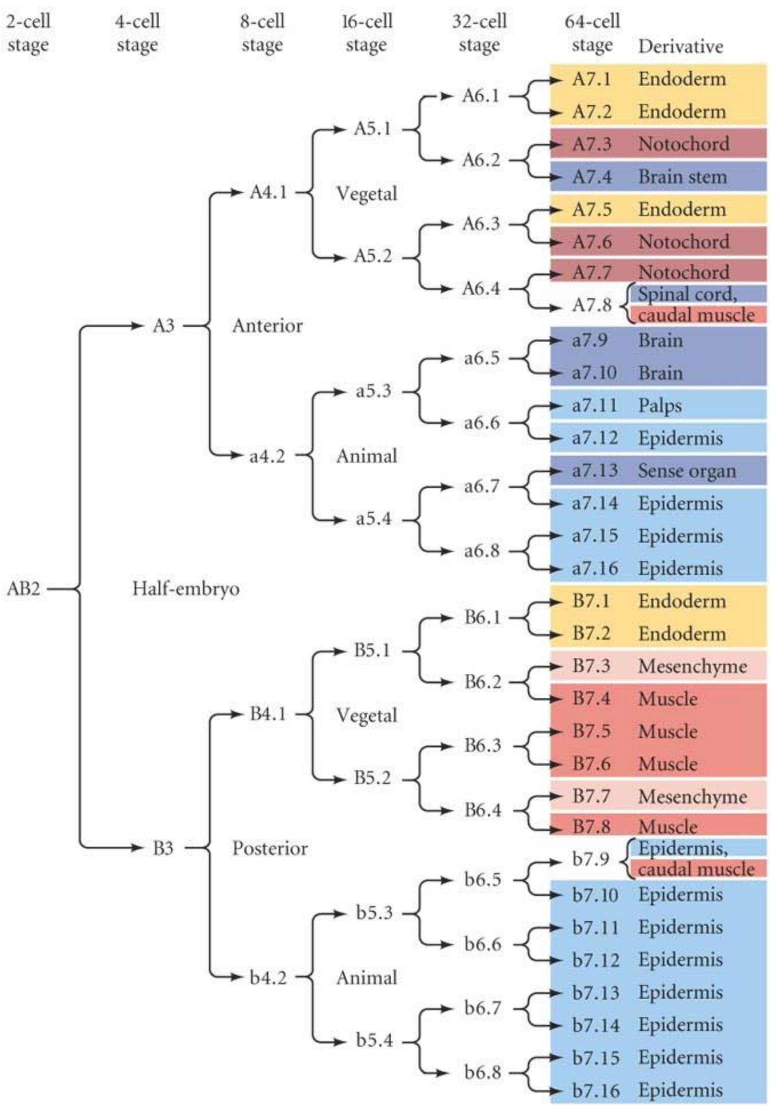


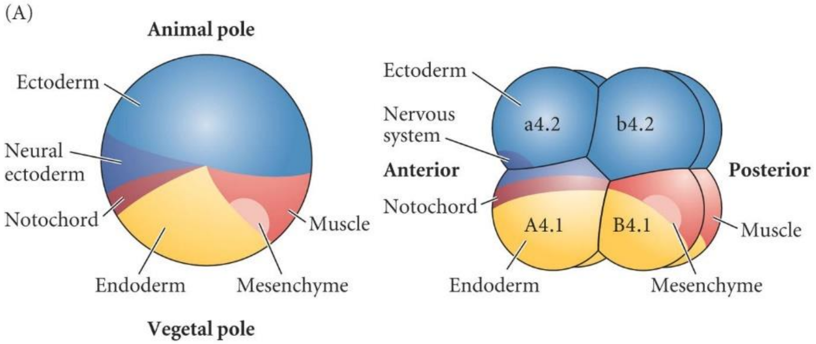


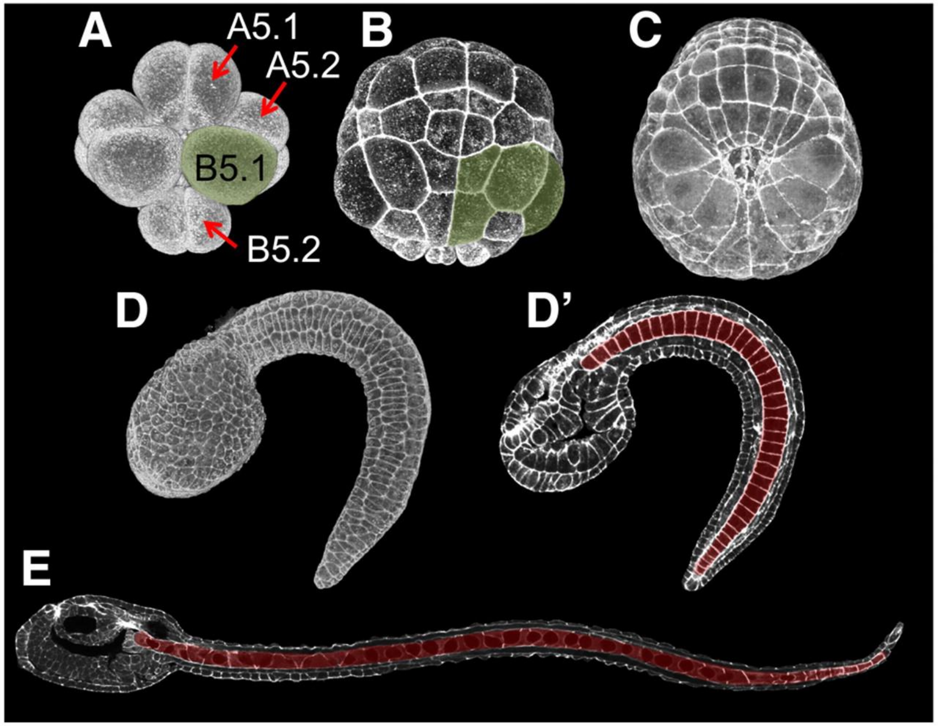
Fate mapping

Invariant

Ascidians (Ciona)





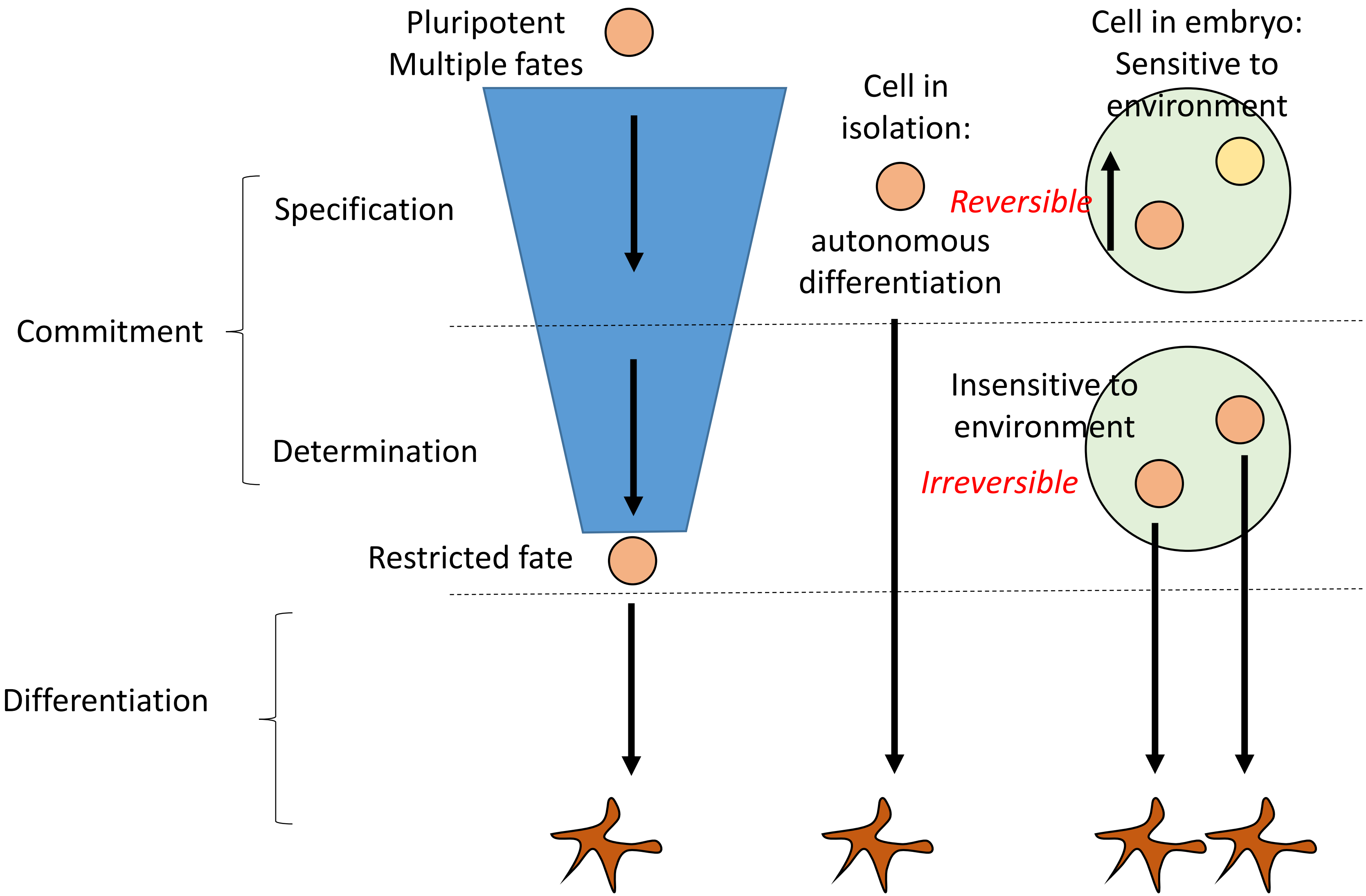


Patrick Lemaire Development 2011;138:2143-2152

DEVELOPMENTAL BIOLOGY, Seventh Edition, Figure 1.7 (Part 2) Sinauer Associates, Inc.

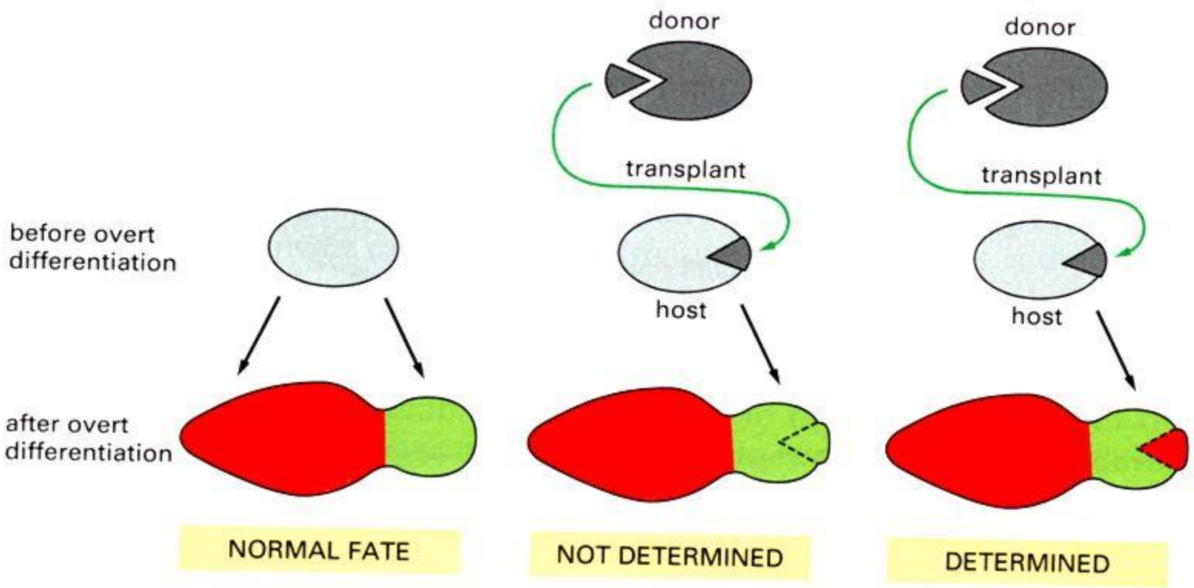
Definitions

Cell fate commitment/specification/determination



Definitions

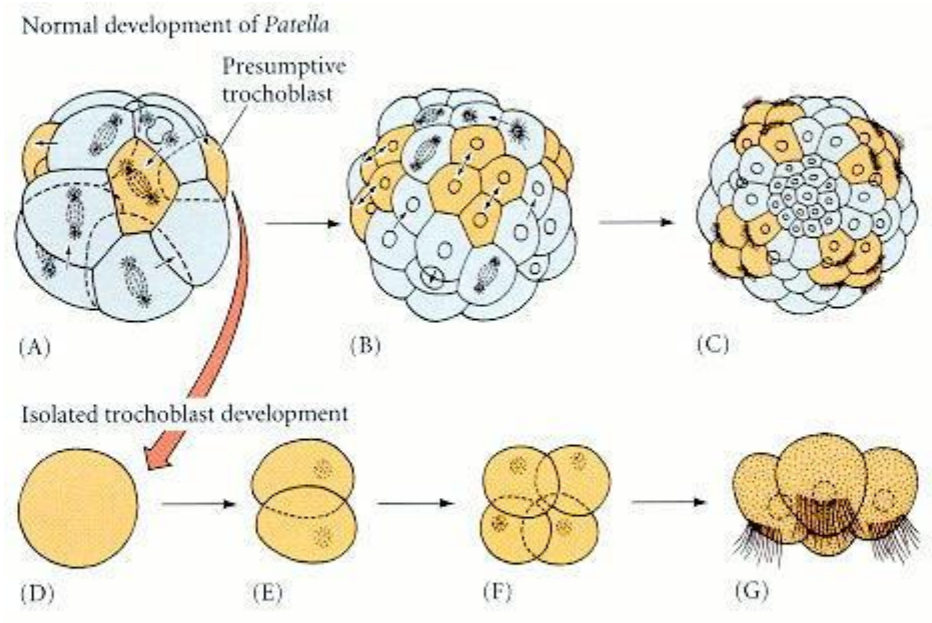
Cell fate determination

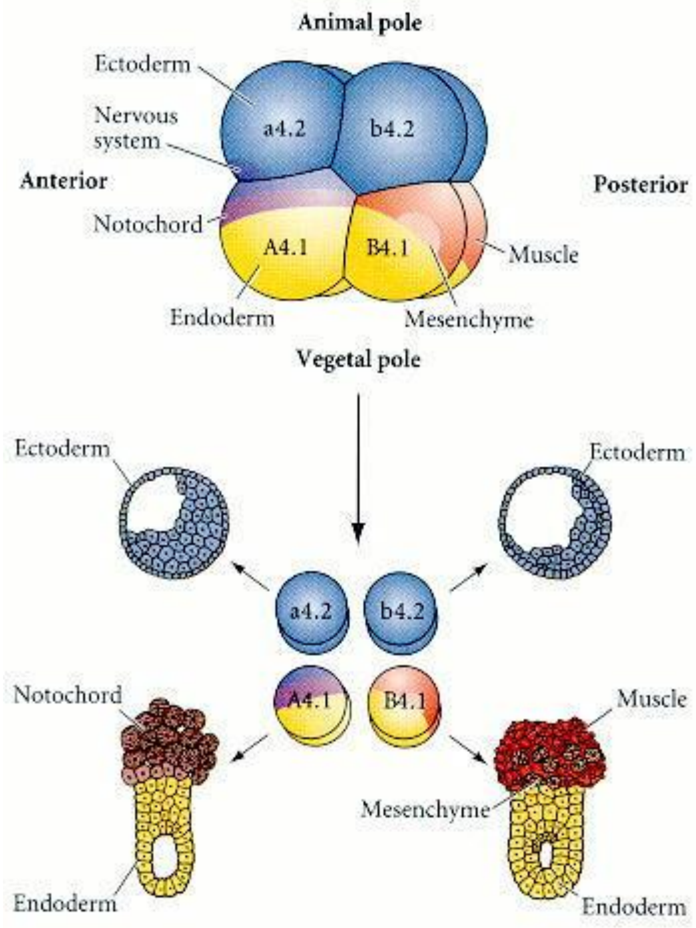


kept together in a cluster, but not if taken singly and isolated from their usual companions.

Definitions

Autonomous specification





Definitions

Conditional specification

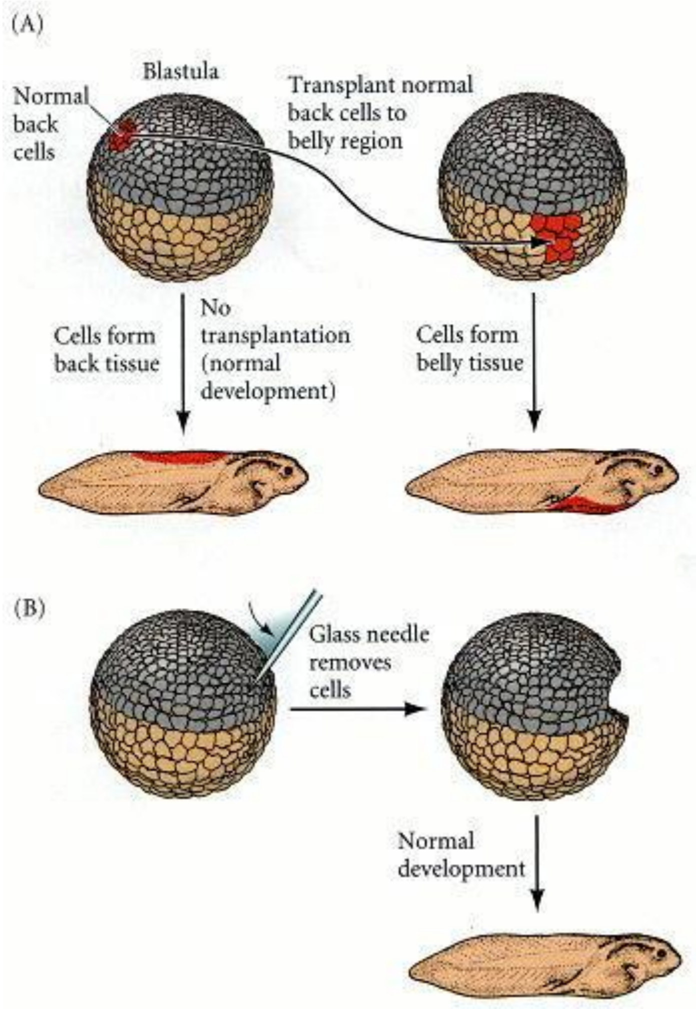


Figure 3.11
Conditional specification. (A) What a cell becomes depends upon its position in the embryo. Its fate is determined by interactions with neighboring cells. (B) If cells are removed from the embryo, the remaining cells can regulate and compensate for the missing part.

Mosaic development

Regulatory development

Table 3.3 Modes of cell type specification and their characteristics

I.	***Autonomous specification***
	Characteristic of most invertebrates.
	Specification by differential acquisitio
	Invariant cleavages produce the same
	Cell type specification precedes any large-scale embryonic cell migration.
	Produces "mosaic" ("determinative") development: cells cannot change fate if a blasto mere is lost.
II.	***Conditional specification***
	Characteristic of all vertebrates and few invertebrates.
	Specification by interactions between cells. Relative positions are important.
	Variable cleavages produce no invariant fate assignments to cells.
	Massive cell rearrangements and migrations precede or accompany specification.
	Capacity for "regulative" development: allows cells to acquire different functions.
III.	***Syncytial specification***
	Characteristic of most insect classes.
	Specification of body regions by interactions between cytoplasmic regions prior to cellularization of the blastoderm.
	Variable cleavage produces no rigid cell fates for particular nuclei.
	After cellularization, conditional specification is most often seen.

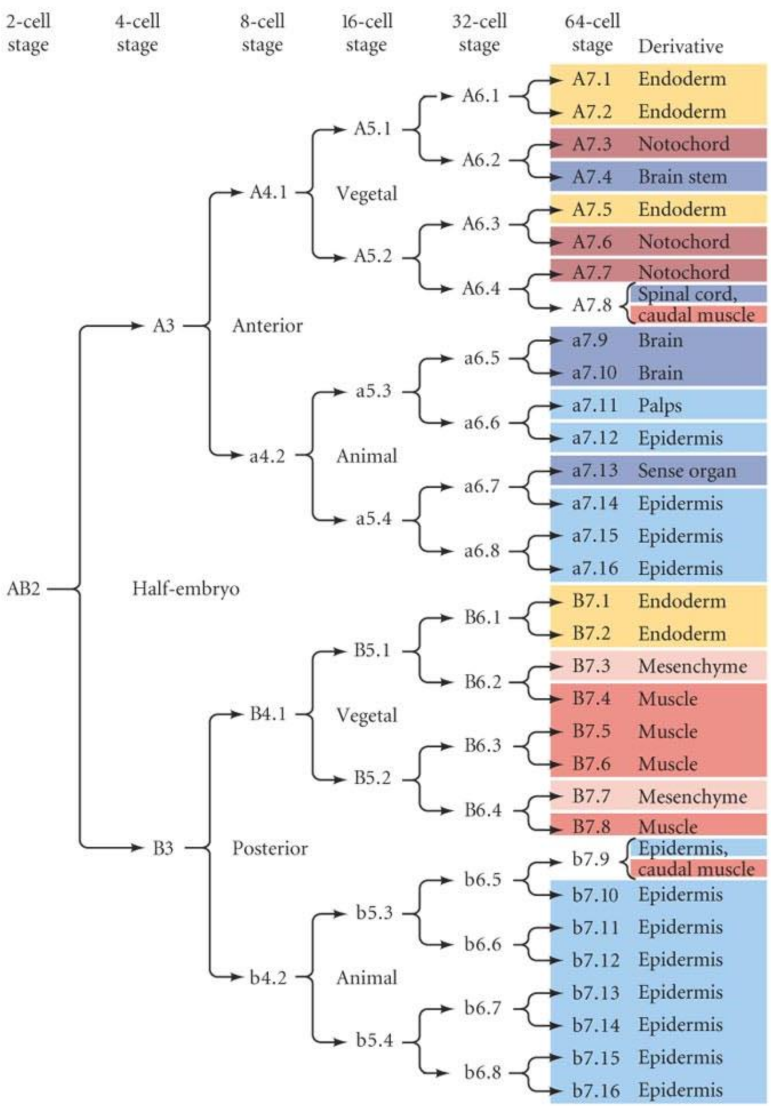
! Invariant cleavage may not exclude conditional specification!

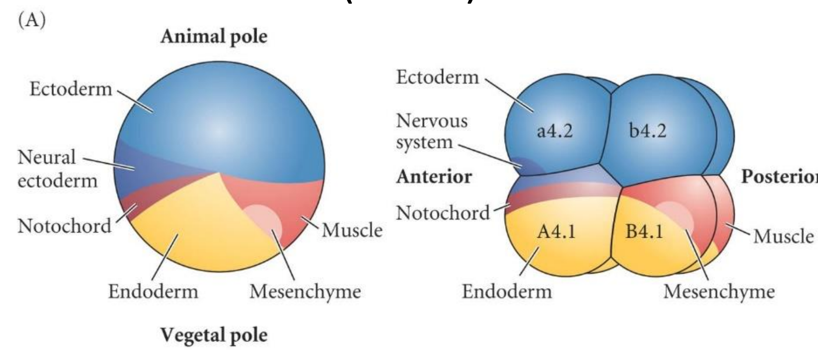
Even if no "regulation", it also does not exclude cell-cell communication

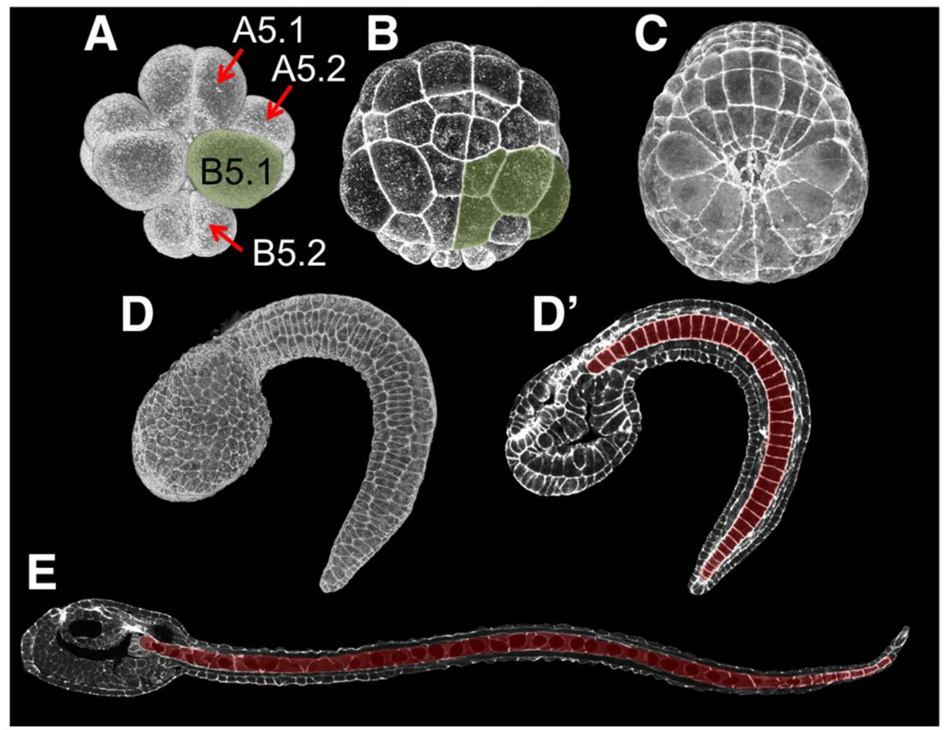
Fate mapping

Invariant, yet cells signal to each other!

Ascidians (Ciona)







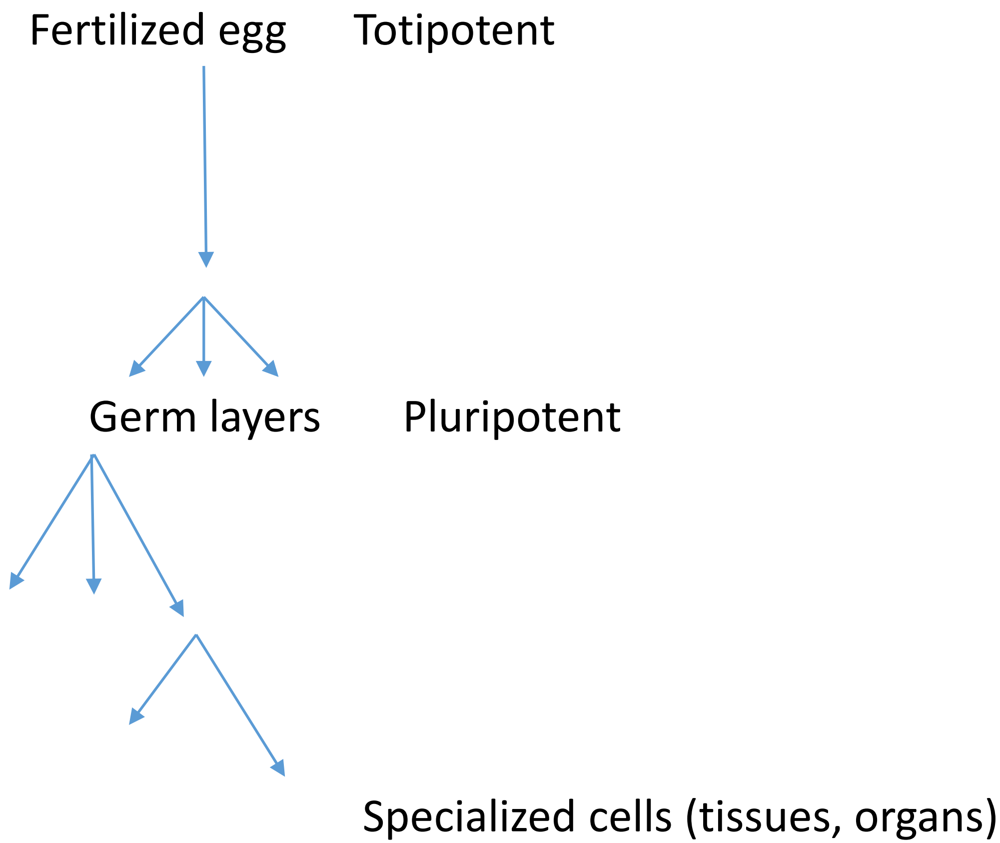
Patrick Lemaire Development 2011;138:2143-2152

DEVELOPMENTAL BIOLOGY, Seventh Edition, Figure 1.7 (Part 2) Sinauer Associates, Inc.

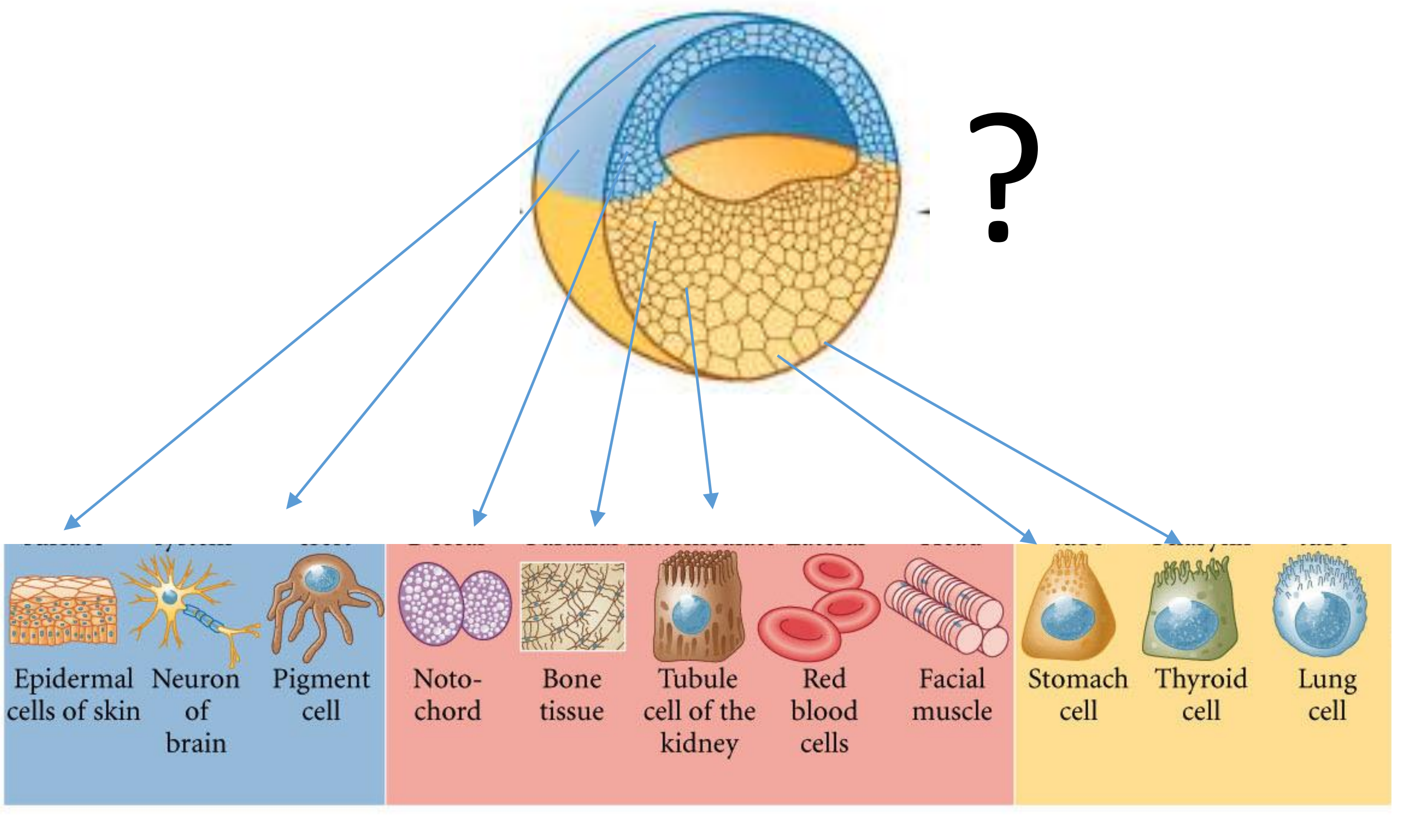
Introduction to cell fate and plasticity during embryonic development

Introduction, fate maps, definitions
Cell determination = multistep process (ex: muscle)
Induction
Morphogens (ex: BMP)
Combinatorial control
Competence
Lateral inhibition
Asymmetric division/asymmetric distribution (germ cells)

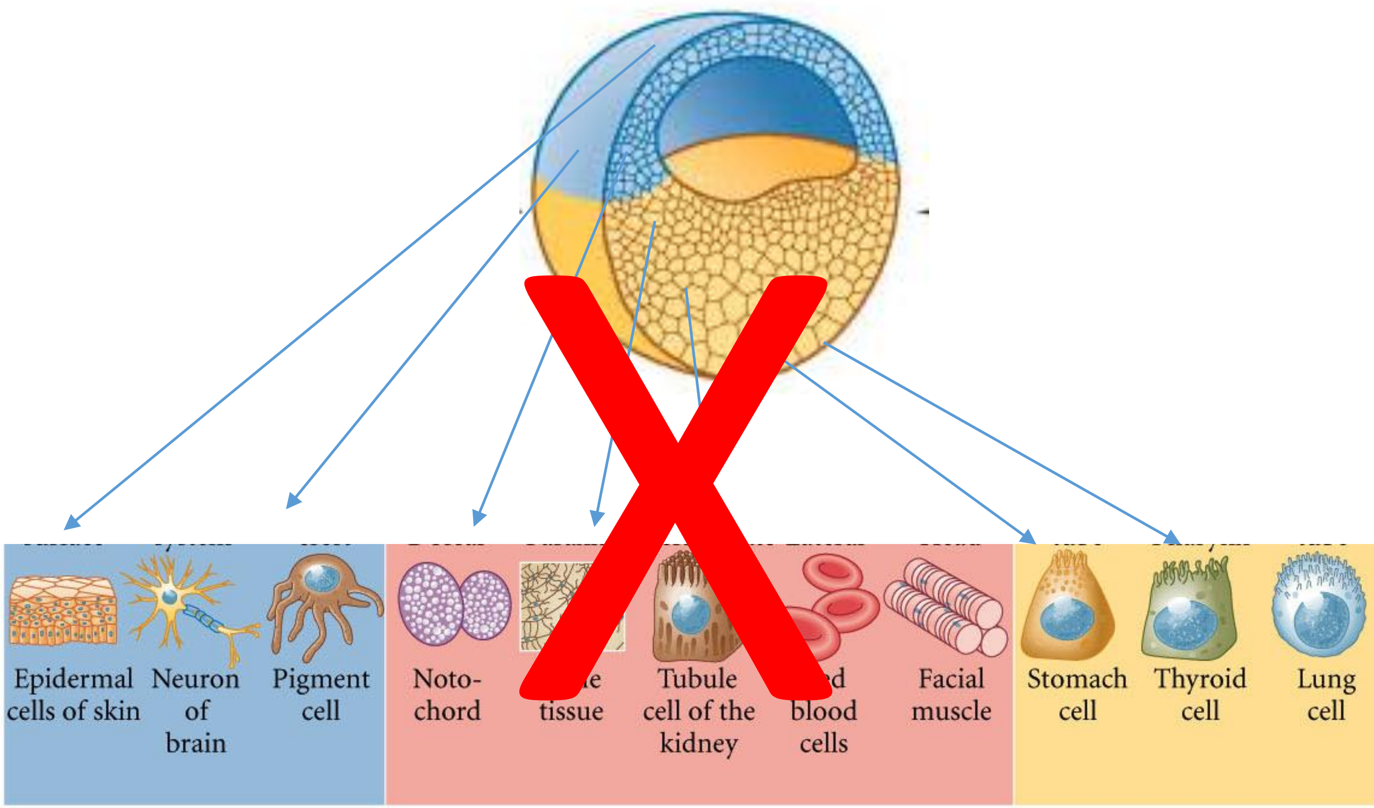
Cell fate determination: a multistep process



Cell fate determination: how does it occur?

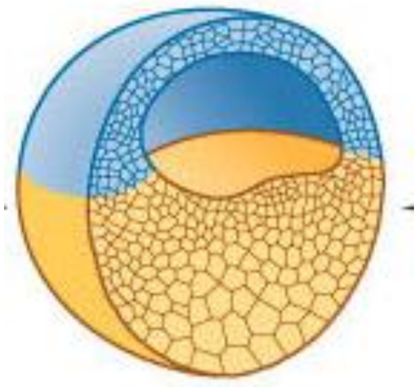


Cell fate determination: a multistep process



Cell fate determination: a multistep process

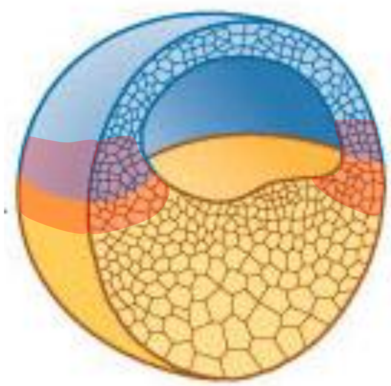
Animal



Vegetal

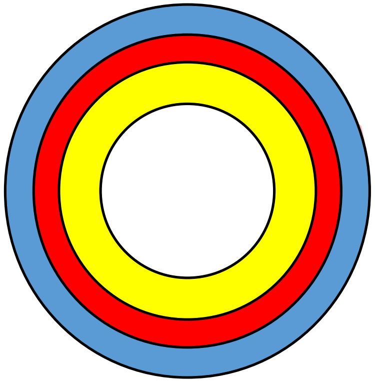
Cell fate determination: a multistep process

Germ layers



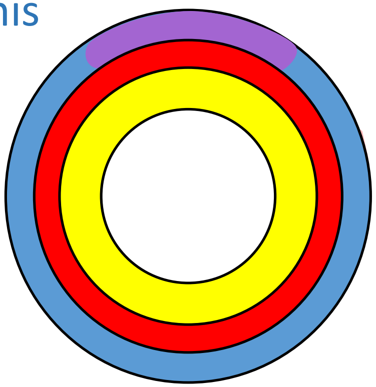
Cell fate determination: a multistep process

Germ layers

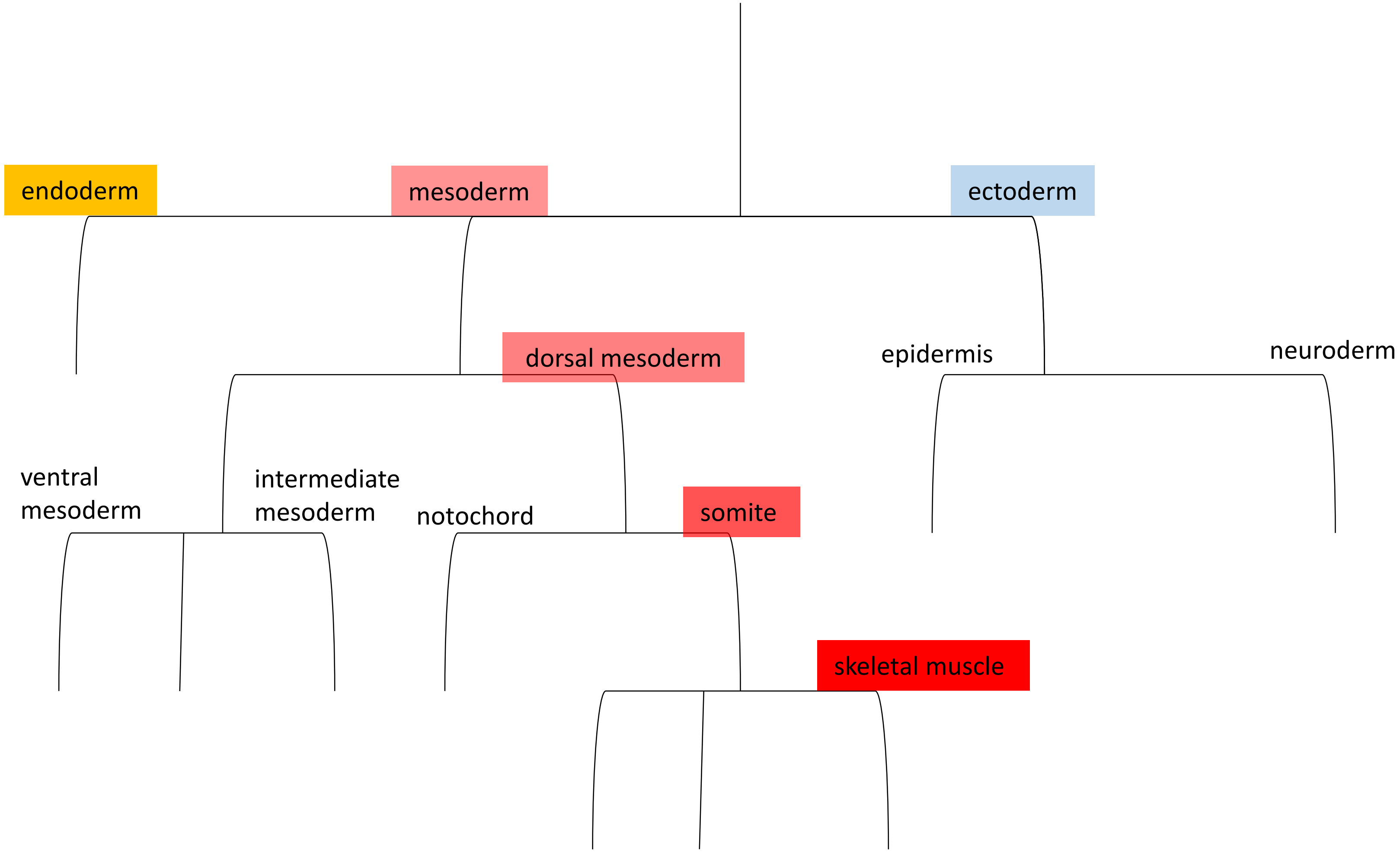


Cell fate determination: a multistep process

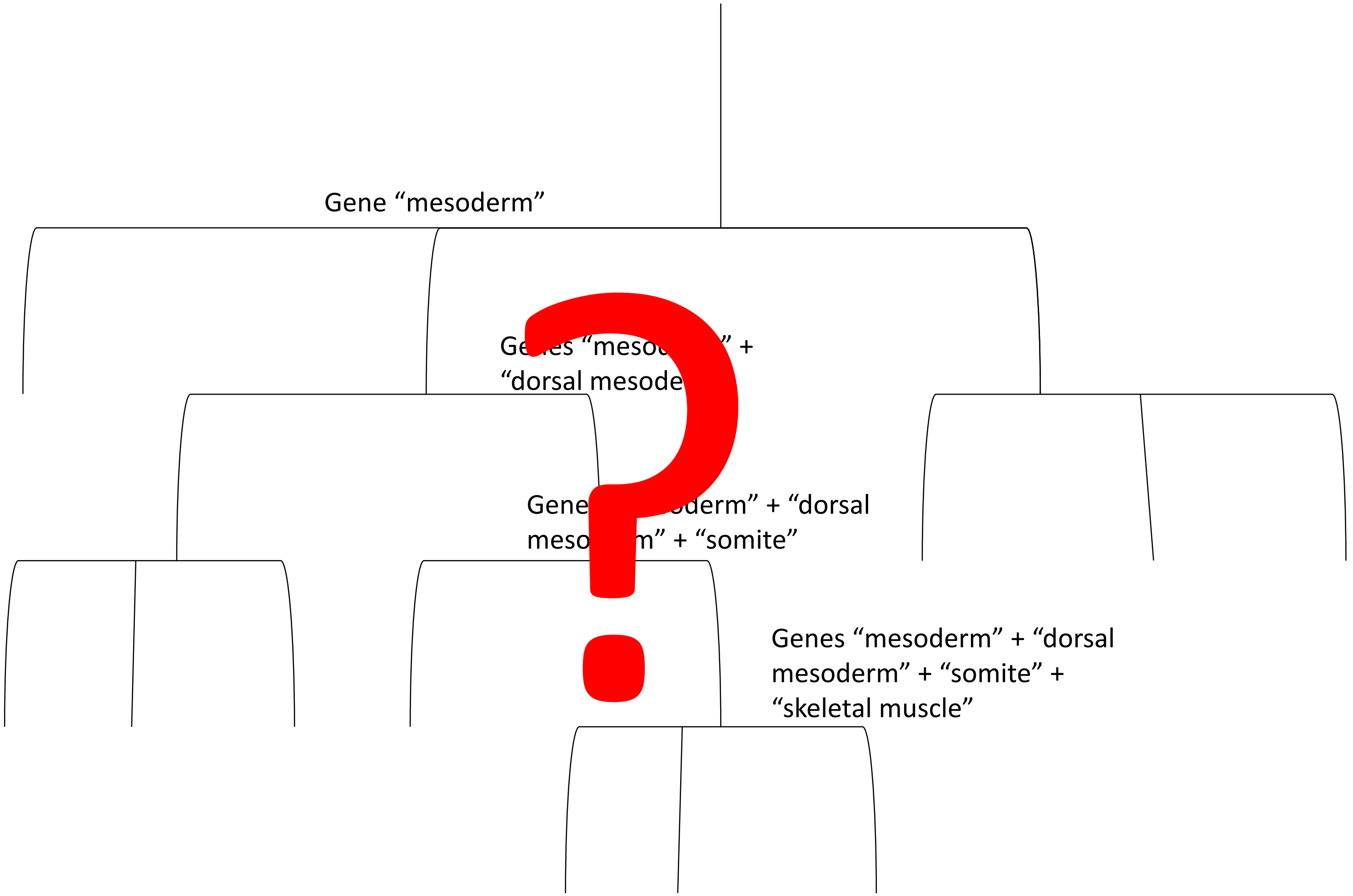
Germ layers



Cell fate determination: a multistep process

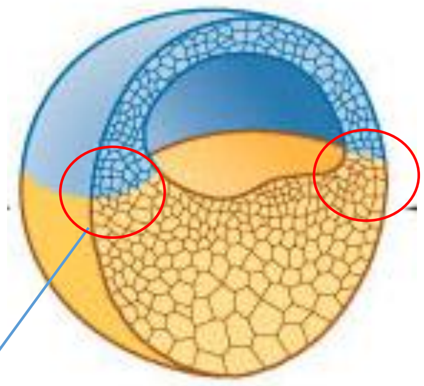


Cell fate determination: a multistep process



Cell fate determination: a multistep process

Prospective mesoderm region

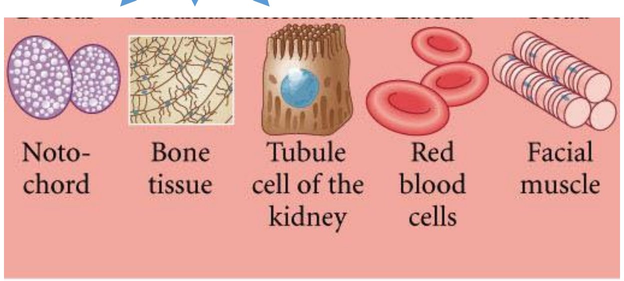


"state A"

Function can be transient during development (example: gastrulation movements)

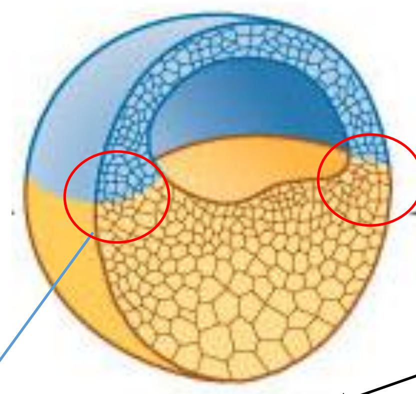
"state B"

"states C1,C2,C3"



Cell fate determination: a multistep process

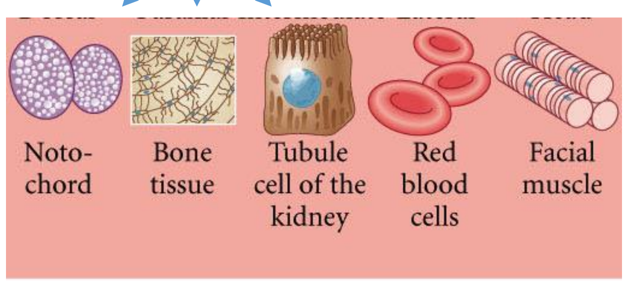
Prospective mesoderm region



"state A"

"state B"

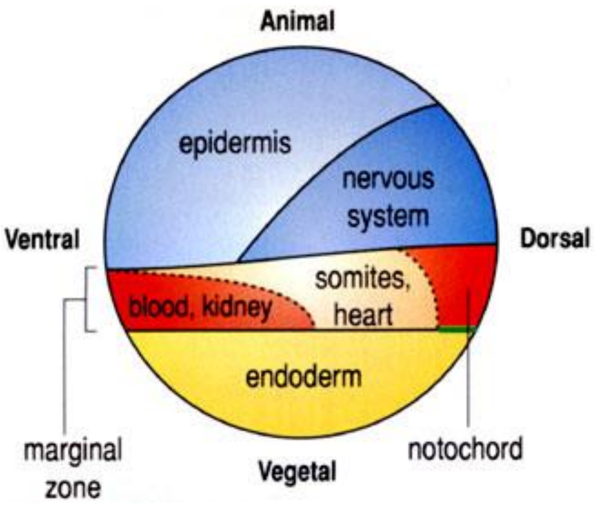
"states C1,C2,C3"

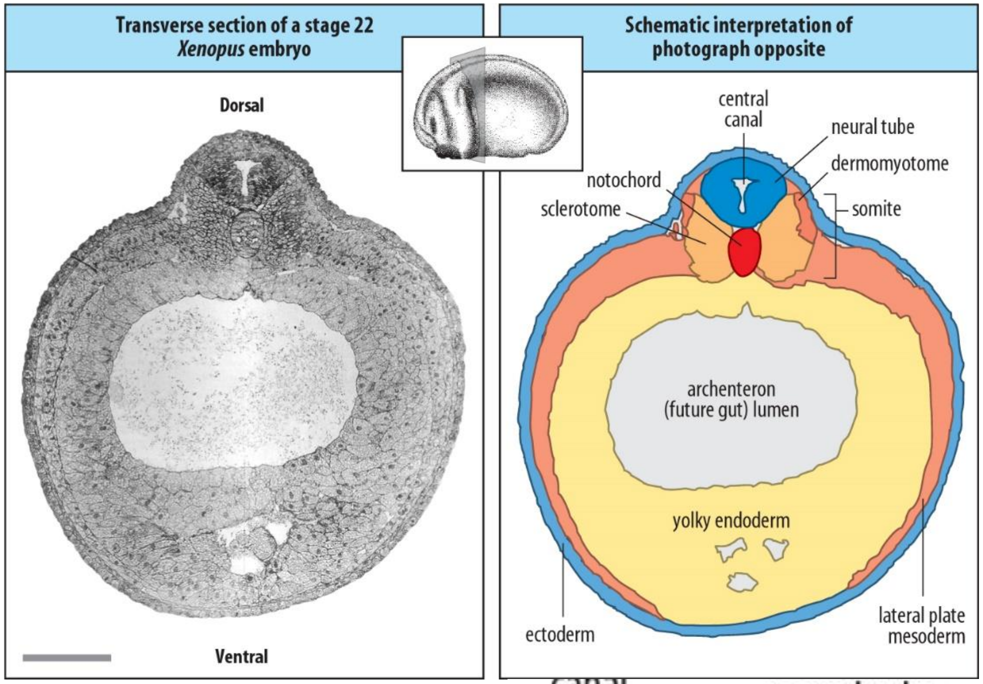


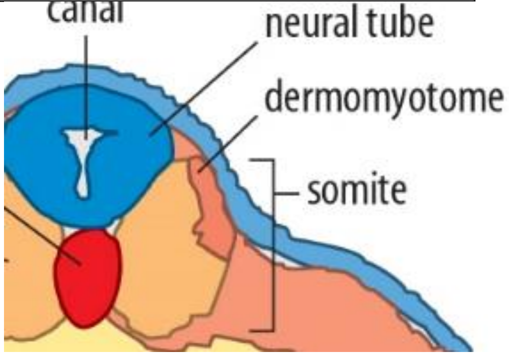
Genes:

- lineage-specific
- "state A-specific", function specific for this particular stage/region
- shared with other lineages
- common to many stages/regions /lineages

Cell fate determination: a multistep process
Example: Skeletal muscle

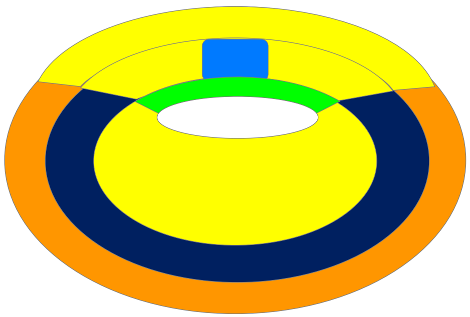




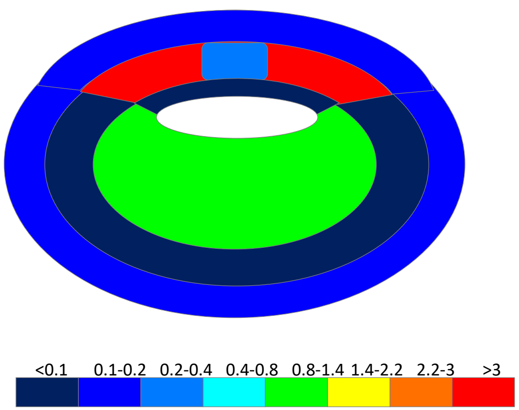


Cell fate determination: a multistep process
Example: Skeletal muscle

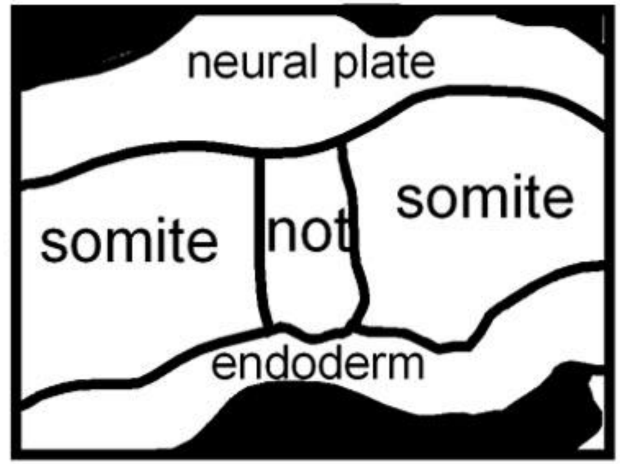
ephrinB1 mRNA levels



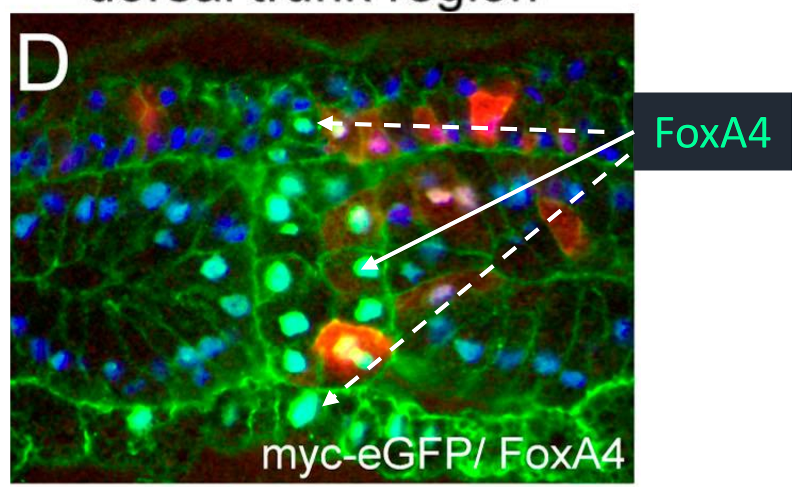
EphB4 mRNA levels



Fagotto, Winklbauer and Rohani, Cell Adh. Migr. 2015

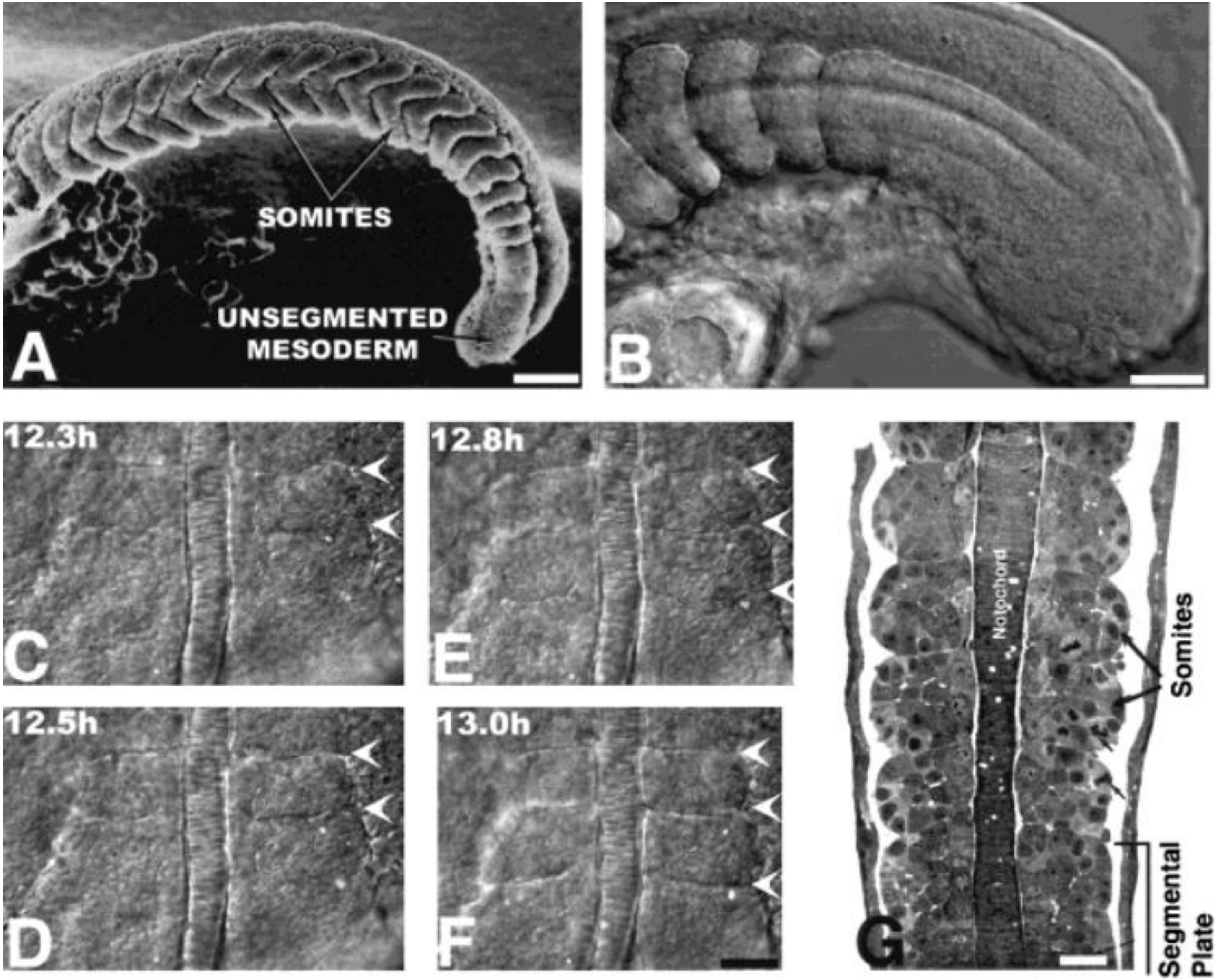


cross-section,
dorsal trunk region

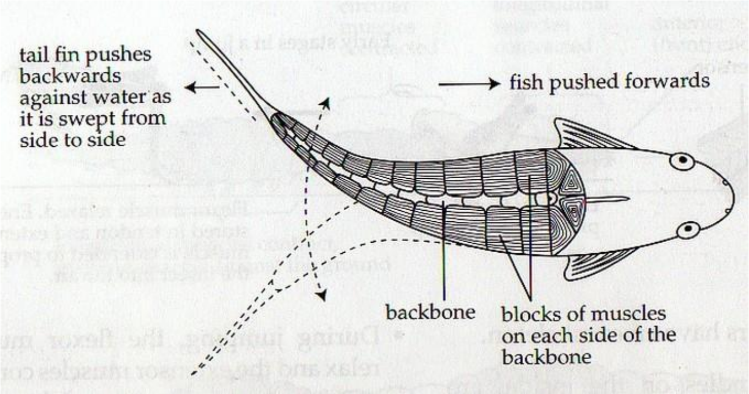


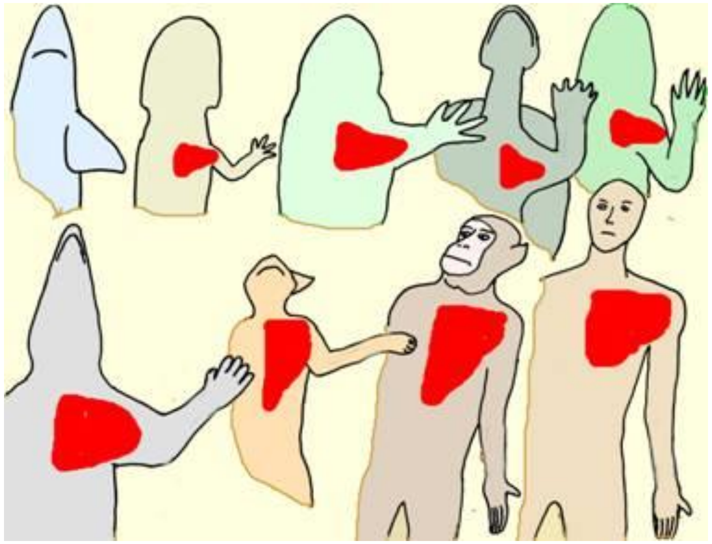
Reintsch, Habring-Muller, Wang, Schohl, Fagotto, Journal of Cell Biology, 2005

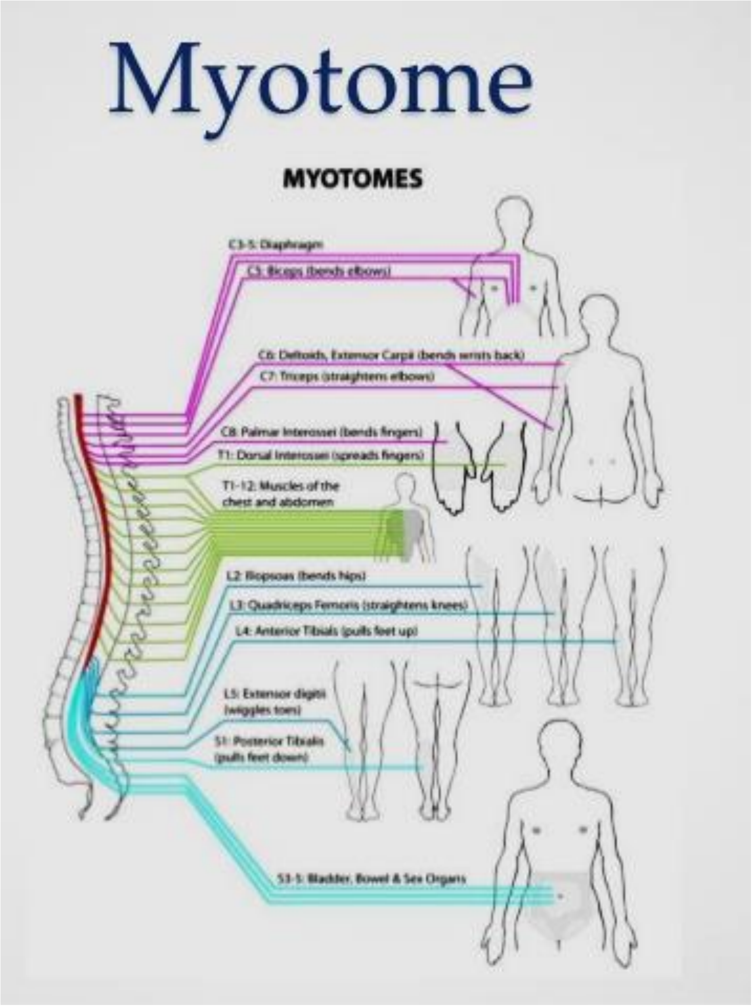
Skeletal muscle: Somitogenesis and myogenesis



Skeletal muscle: Somitogenesis and myogenesis







Skeletal muscle: Somitogenesis and myogenesis

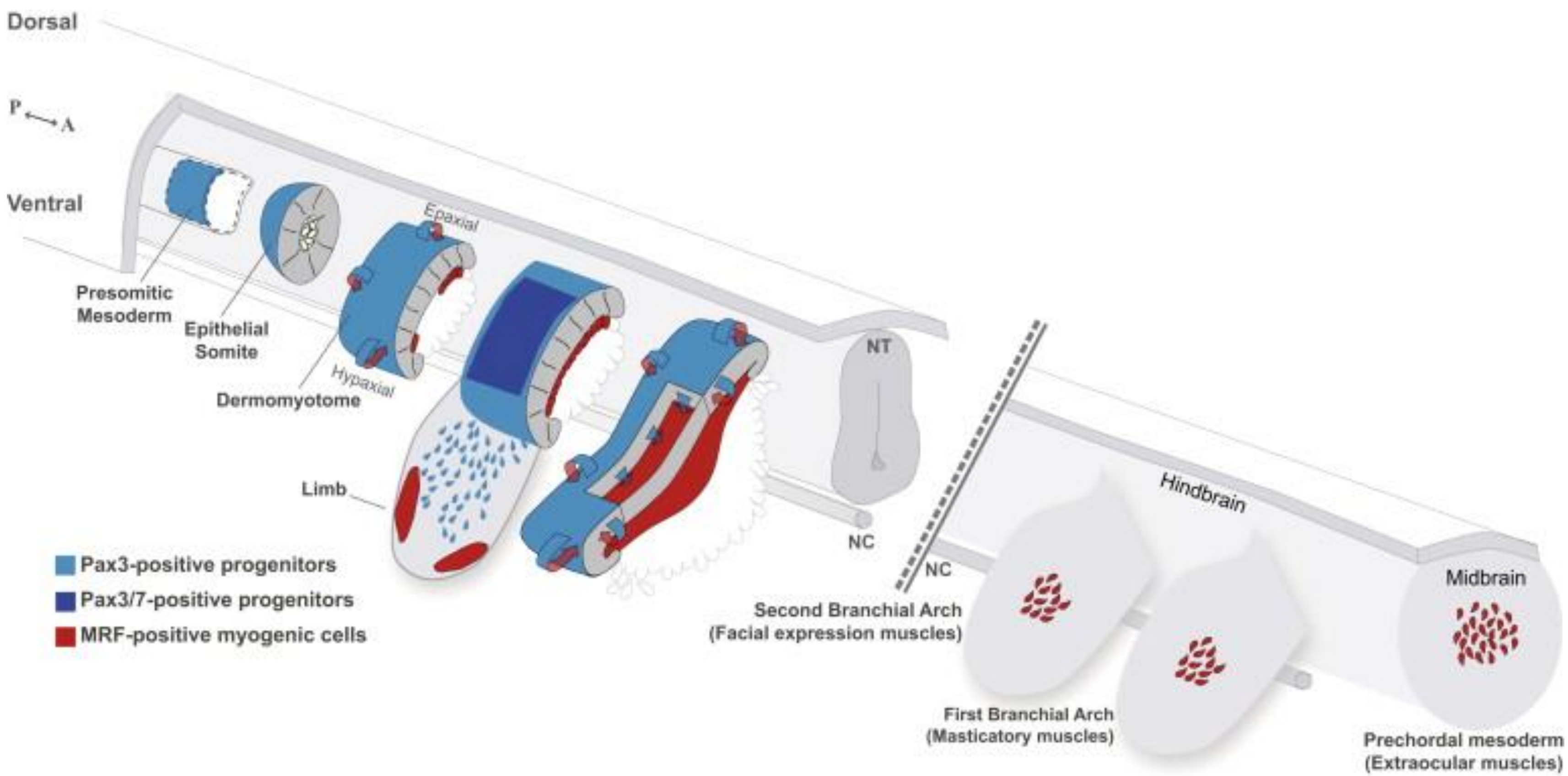


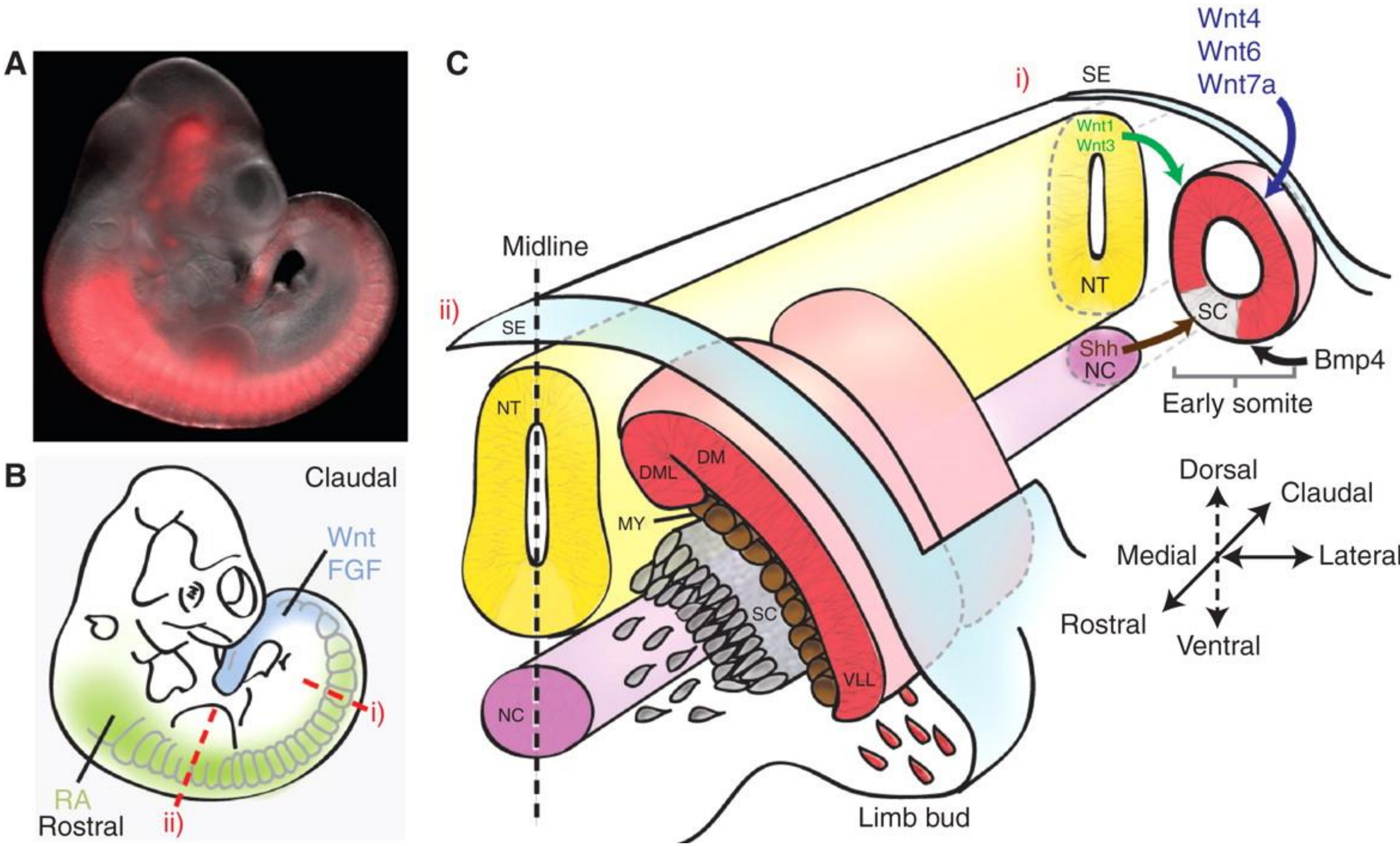
Figure 1. Schematic Representation of Somites, First and Second Branchial Arches, and Prechordal Mesoderm that Are the Sources of Skeletal Muscles, Shown for the Mouse Embryo Somites mature following an anterior (A) to posterior (P) developmental gradient. NT, neural tube; NC, notochord.

Margaret Buckingham, Peter W.J. Rigby

Gene Regulatory Networks and Transcriptional Mechanisms that Control Myogenesis

http://dx.doi.org/10.1016/j.devcel.2013.12.020

Embryonic myogenesis (mouse)



C. Florian Bentzinger et al. Cold Spring Harb Perspect Biol 2012;4:a008342

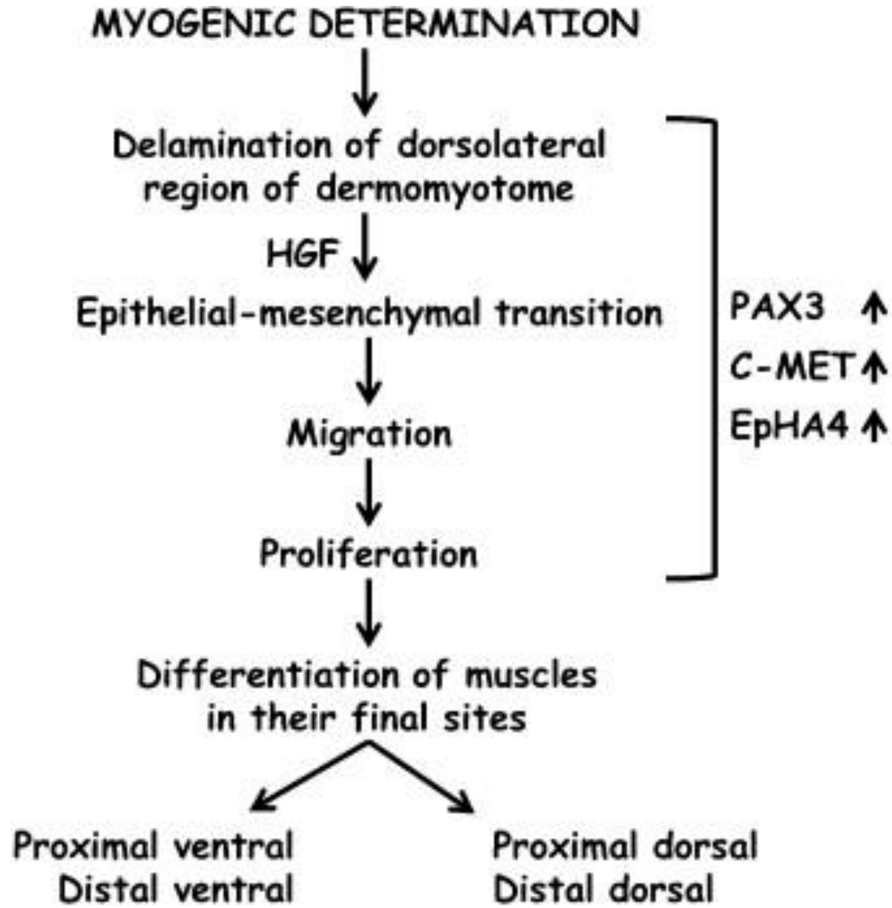


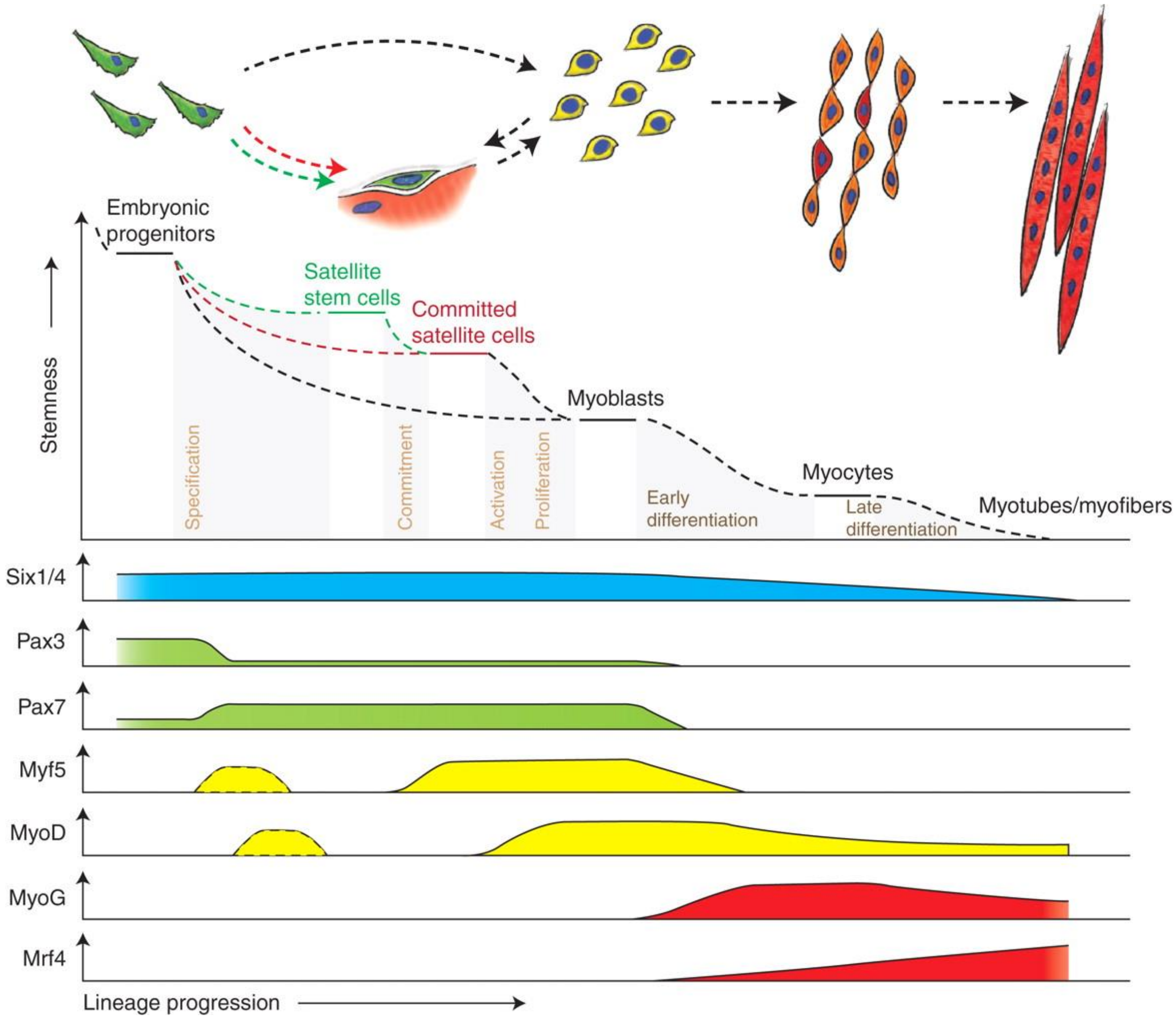
Fig. 12. Molecular signals involved in the development of limbs muscles.

Giuseppe Musumeci, Paola Castrogiovanni, Raymond Coleman, Marta Anna Szychlinska, Lucia Salvatorelli, Rosalba Parenti, Gaetano Magro, Rosa Imbesi

Somitogenesis: From somite to skeletal muscle

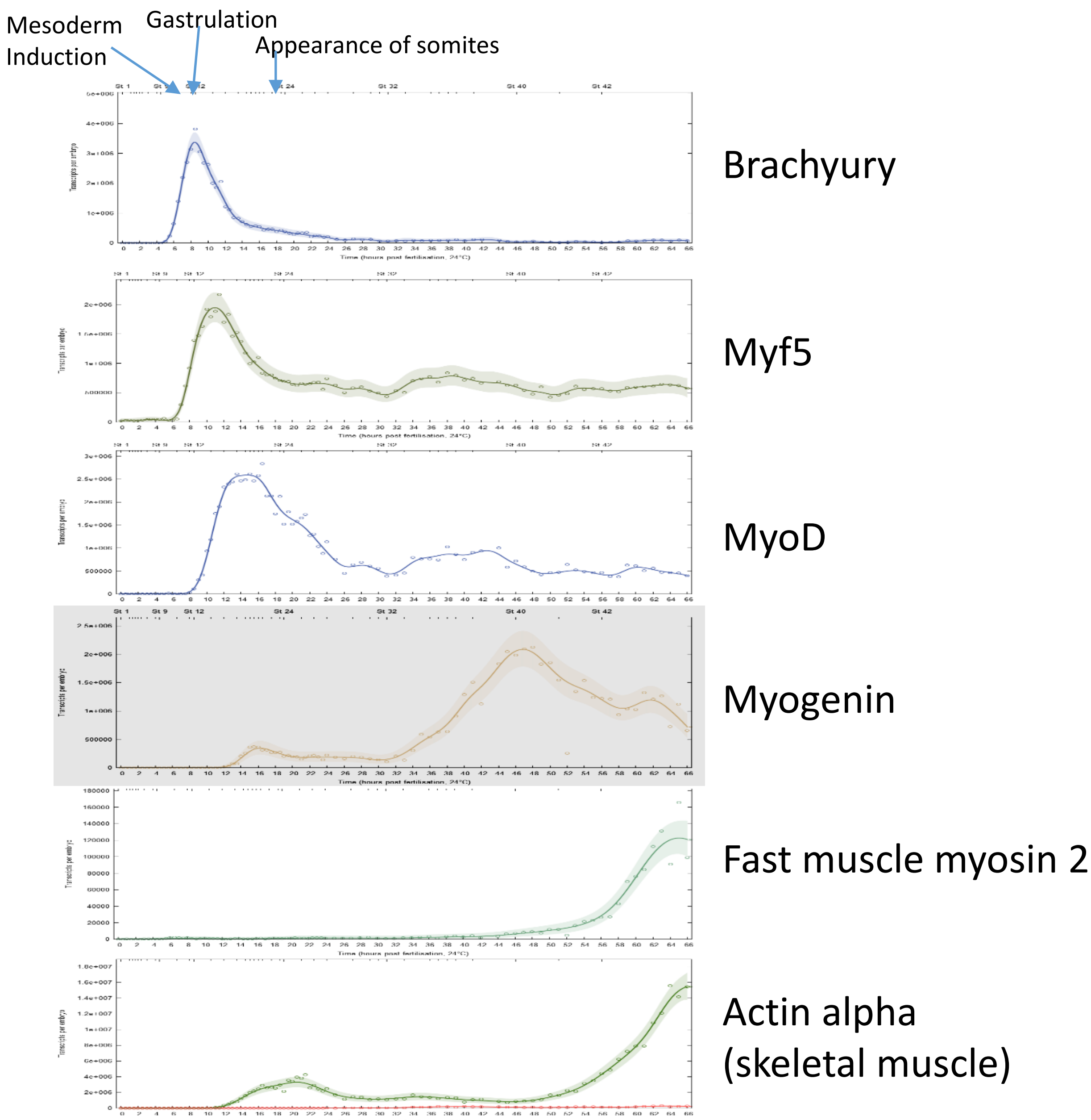
Acta Histochemica, Volume 117, Issues 4–5, 2015, 313–328
http://dx.doi.org/10.1016/j.acthis.2015.02.011

Hierarchy of transcription factors regulating progression through the myogenic lineage (mouse).



C. Florian Bentzinger et al. Cold Spring Harb Perspect Biol 2012;4:a008342

Time course of muscle specific genes during Xenopus development



Time course of muscle specific genes during Xenopus development

Mesoderm Induction

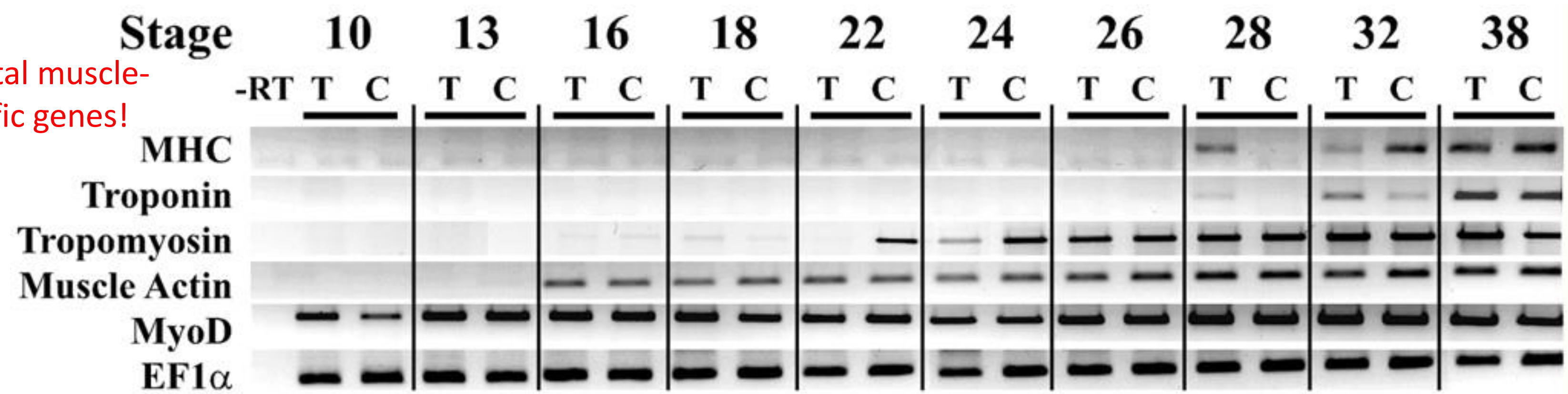
Gastrulation

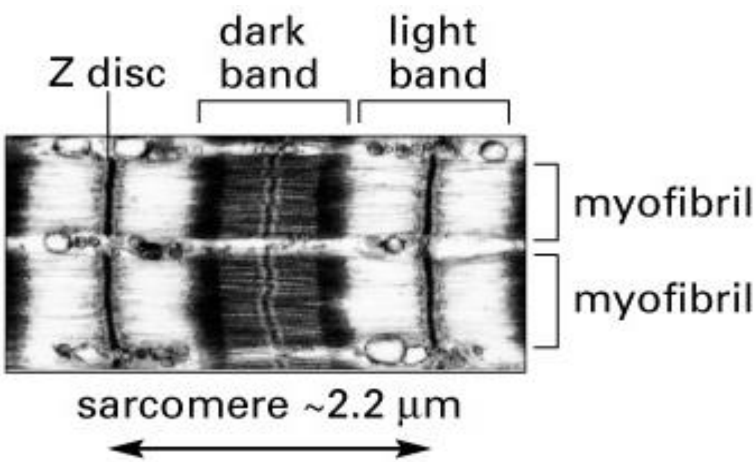
Paraxial mesoderm specification

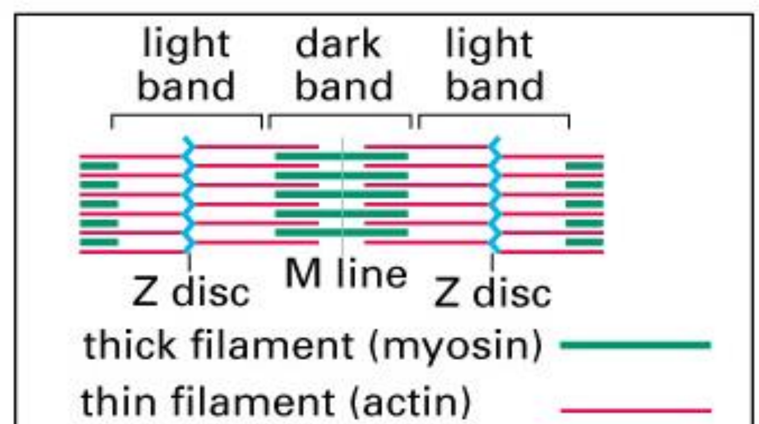
Appearance of somites

Tadpole hatching
Muscle activity

Skeletal muscle-specific genes!





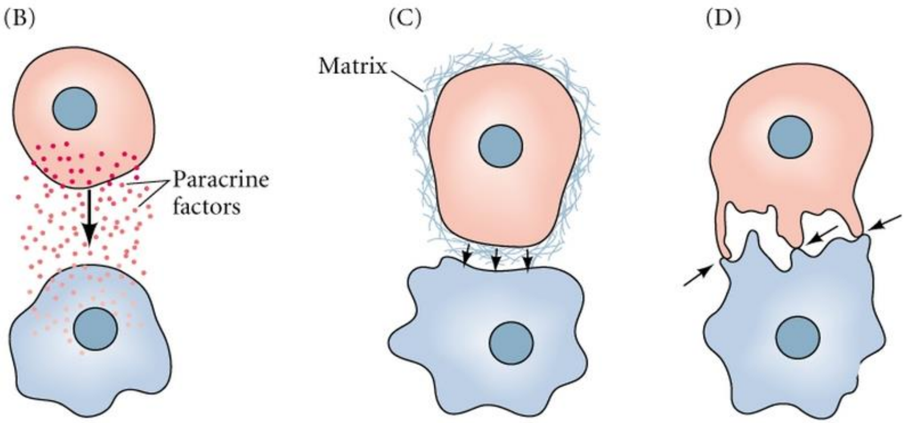


Introduction to cell fate and plasticity during embryonic development

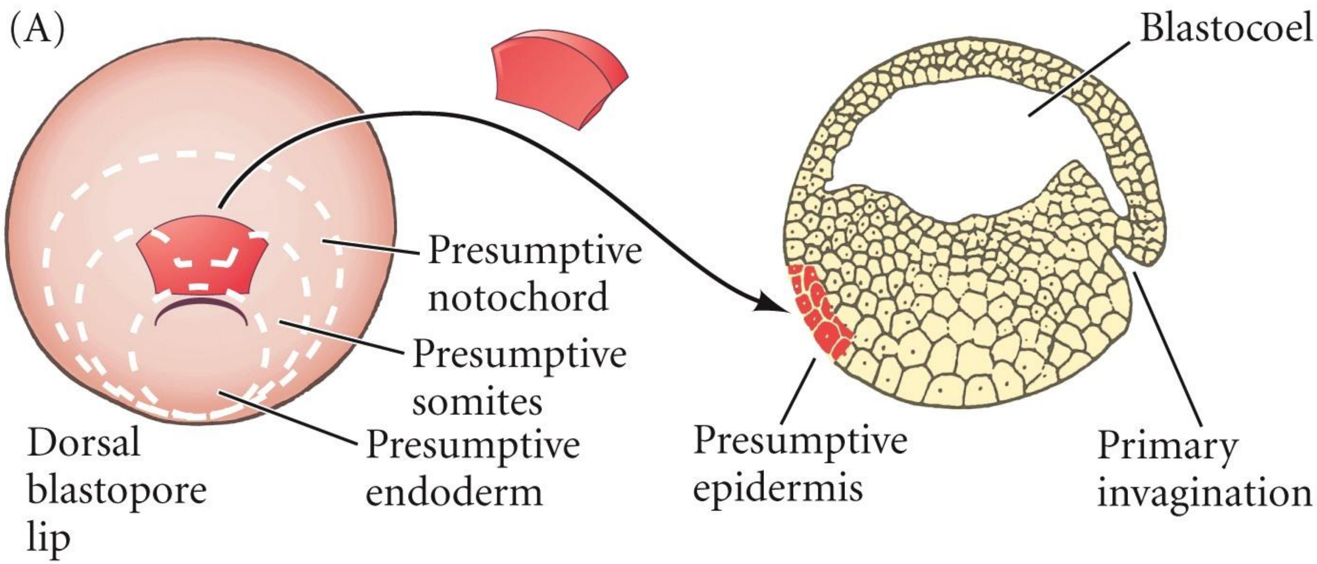
Introduction, fate maps, definitions
Cell determination = multistep process (ex: muscle)
Induction
Morphogens (ex: BMP)
Combinatorial control
Competence
Lateral inhibition
Asymmetric division/asymmetric distribution (germ cells)

Induction

Extrinsic signaling



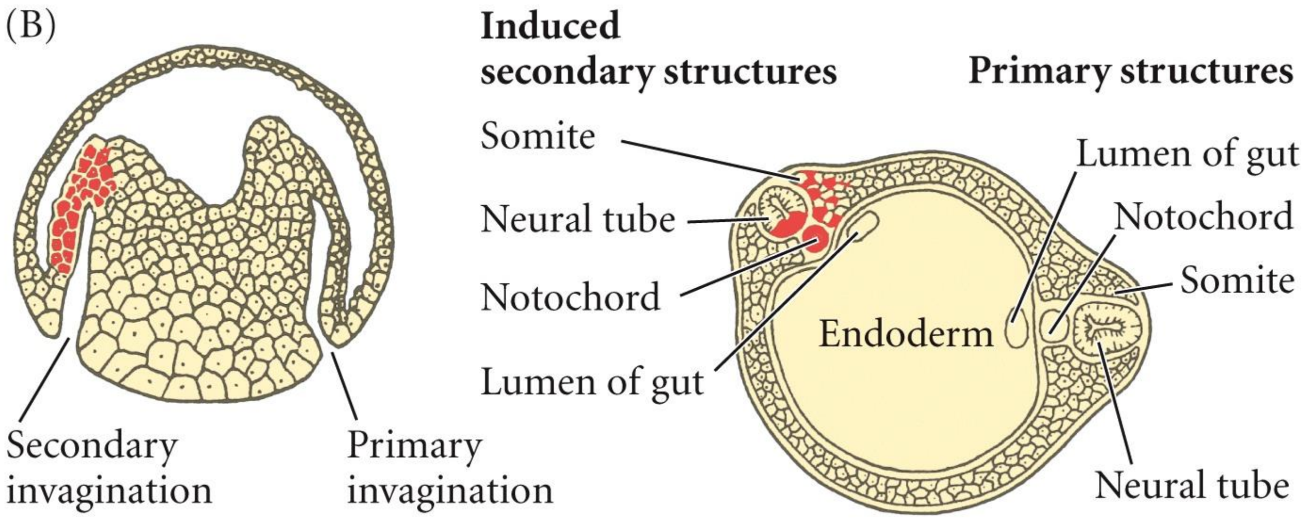
Organization of a secondary axis by dorsal blastopore lip tissue



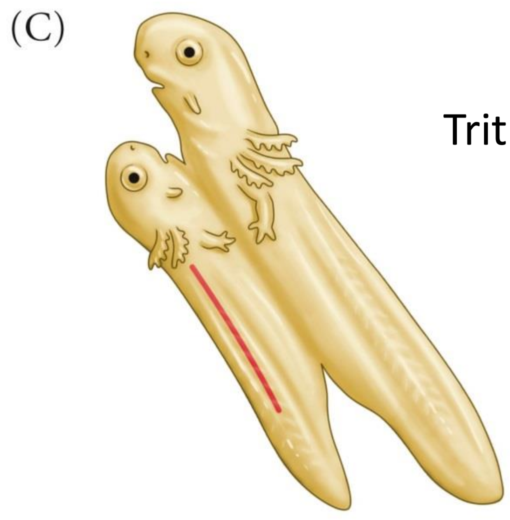
DEVELOPMENTAL BIOLOGY 10e, **Figure 8.18 (Part 1)**

Mangold and
Spemann, 1924

Organization of a secondary axis by dorsal blastopore lip tissue



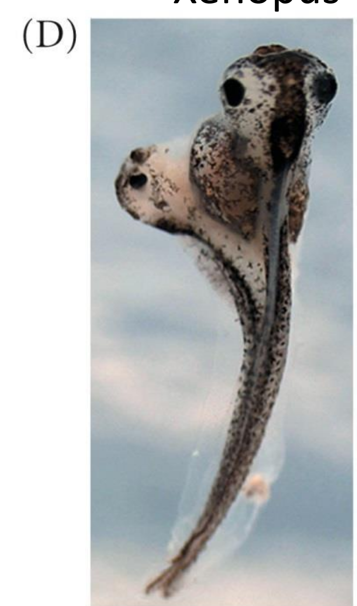
DEVELOPMENTAL BIOLOGY 10e, **Figure 8.18 (Part 2)**



Triturus

DEVELOPMENTAL BIOLOGY 10e, **Figure 8.18 (Part 3)**

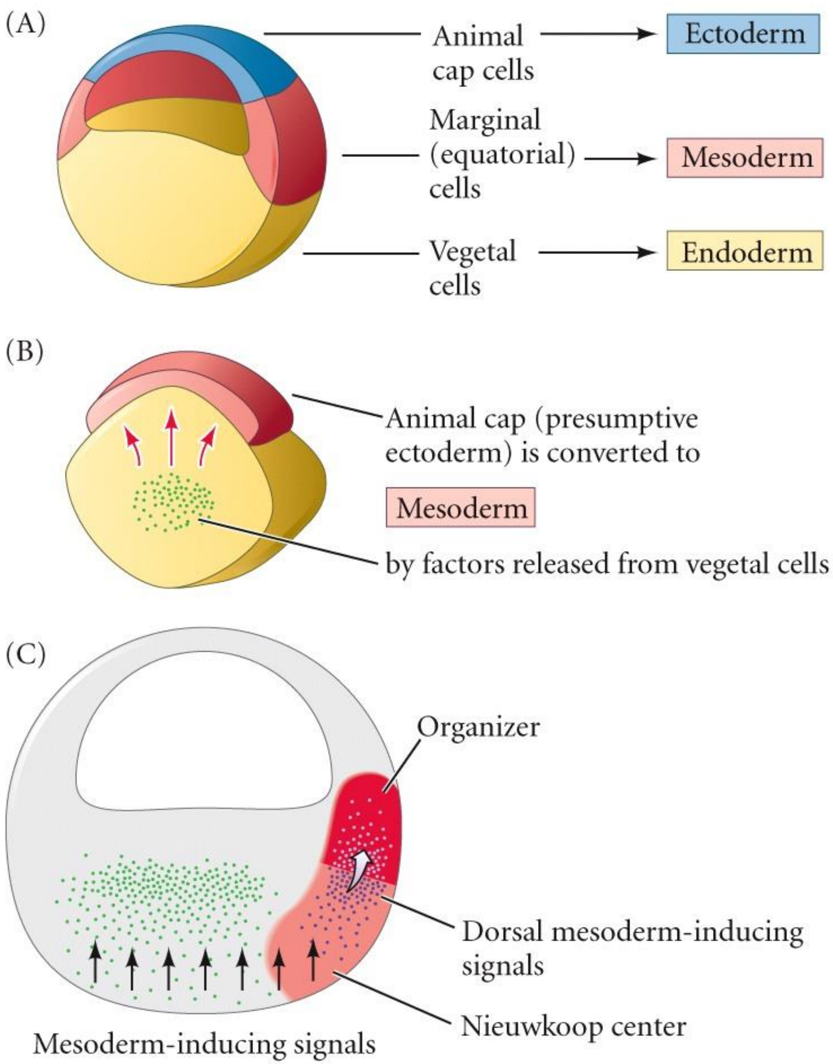
Xenopus



DEVELOPMENTAL BIOLOGY 10e, **Figure 8.18 (Part 4)**

Mesodermal induction

Nieuwkoop and by Nakamura and Takasaki



***DEVELOPMENTAL BIOLOGY 10e*, Figure 8.19**

1) Ectoderm can be induced into mesoderm (and endoderm)
2) Existence of mesoderm inducing signals (in endoderm AND mesoderm)
3) D/V regionalization: anterior endoderm induces anterior mesoderm,… -> Dorsalizing center

Induction

Inductive signals:

Limited number of pathways

Soluble, diffusible factors:

FGF, Wnt, TGFβ, Hedgehog, Retinoic acid

Direct cell contact signaling:

Ephrin-Eph, Delta-Notch

Solutions for complexity:

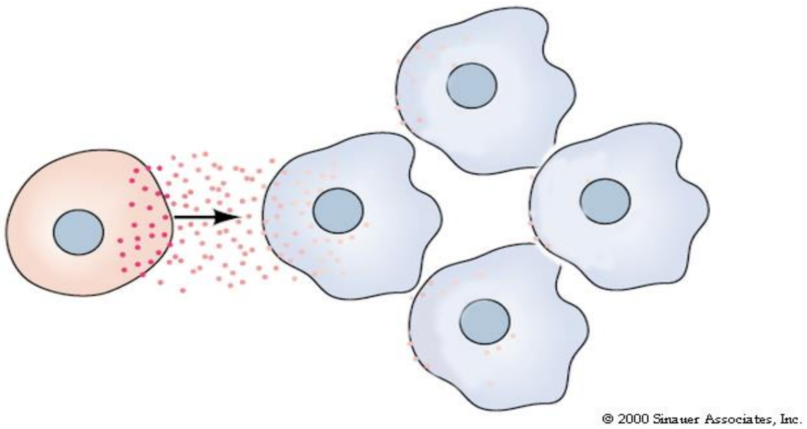
- Sequential use (different context, “competence”)
- Multiple combinations

Introduction to cell fate and plasticity during embryonic development

Introduction, fate maps, definitions
Cell determination = multistep process (ex: muscle)
Induction
Morphogens (ex: BMP)
Combinatorial control
Competence
Lateral inhibition
Asymmetric division/asymmetric distribution (germ cells)

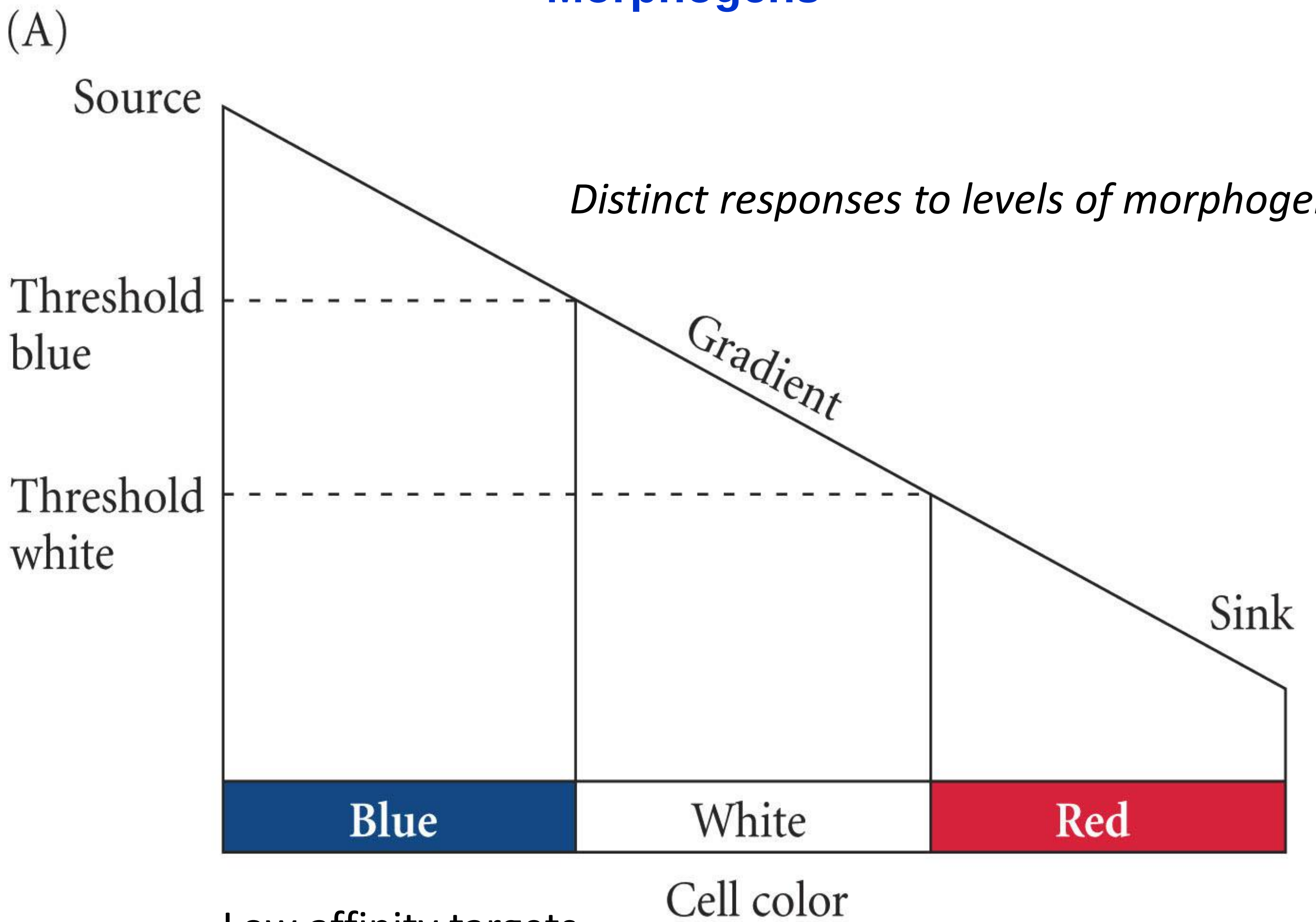
Induction: How to provide spatial information?

Morphogens



Induction: How to provide spatial information?

Morphogens



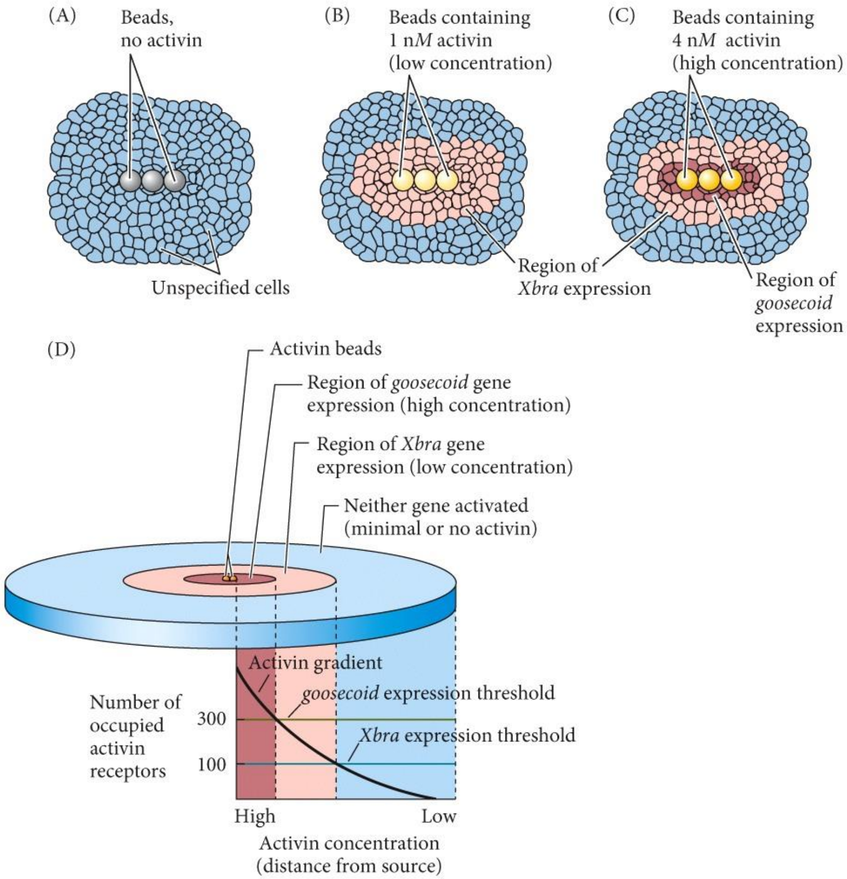
Distinct responses to levels of morphogen

Low affinity targets

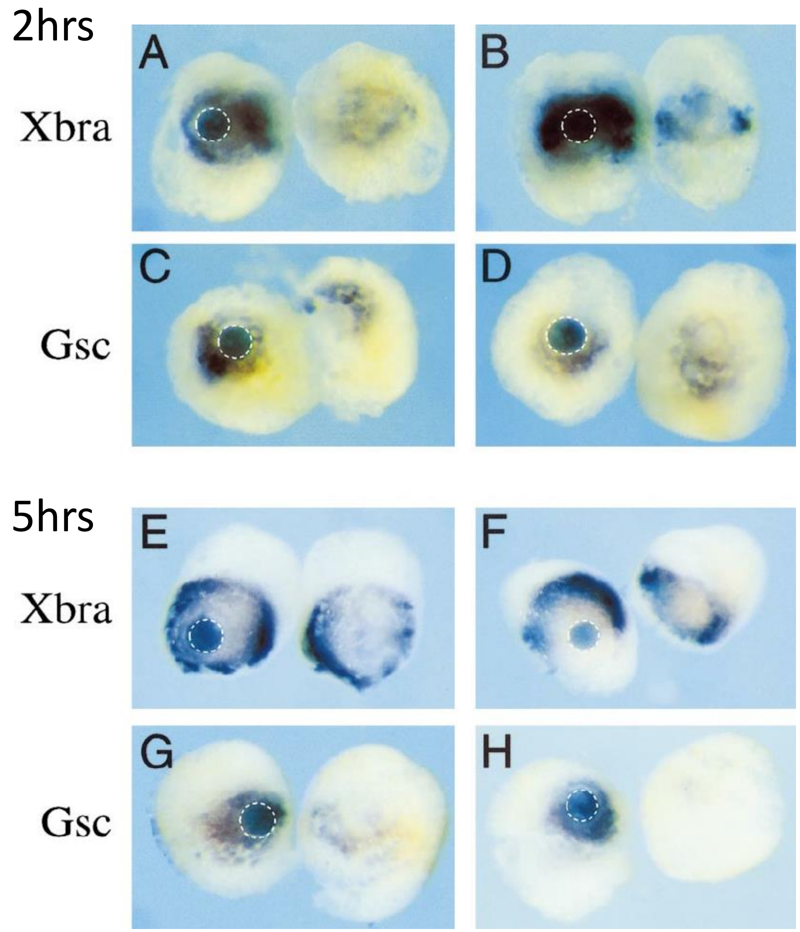
High affinity targets

Induction: How to provide spatial information?

Morphogens



***DEVELOPMENTAL BIOLOGY 10e*, Figure P2.10**



Developmental Biology **217**, 166–172 (2000)
doi:10.1006/dbio.1999.9531, available online at http://www.idealibrary.com on IDEAL®

Gradual Refinement of Activin-Induced Thresholds Requires Protein Synthesis

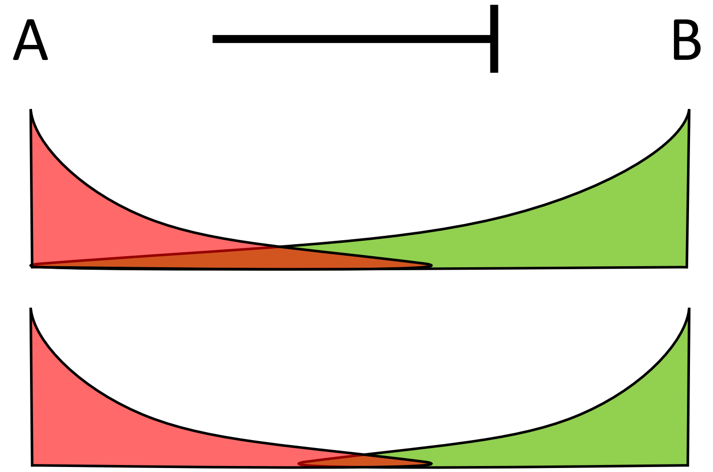
C. Papin and J. C. Smith
Division of Developmental Biology, National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, United Kingdom

FIG. 2. Spatial expression patterns of *Xbra* and *goosecoid* in activin bead sandwiches at different time points. Activin beads incubated in 0.2 units/ml activin were sandwiched between two animal caps. Conjugates were cultured for 2 h (A–D) or 5 h (E–H) until control embryos had reached stage 10.5 or 12. They were then fixed and assayed for expression of *Xbra* (A, B, E, F) or *goosecoid* (C, D, G, H) by *in situ* hybridisation. Two different conjugates are shown for each condition and are representative of at least 20 samples. Each conjugate has been bisected with a tungsten needle after *in situ* hybridisation; dashed white circles indicate the position of the bead. Note that *Xbra* and *goosecoid* are expressed in similar domains in A–D but have resolved to their definitive expression patterns in E–H.

Beyond simple morphogen gradients:

Patterns refinement by diffusible inhibitors

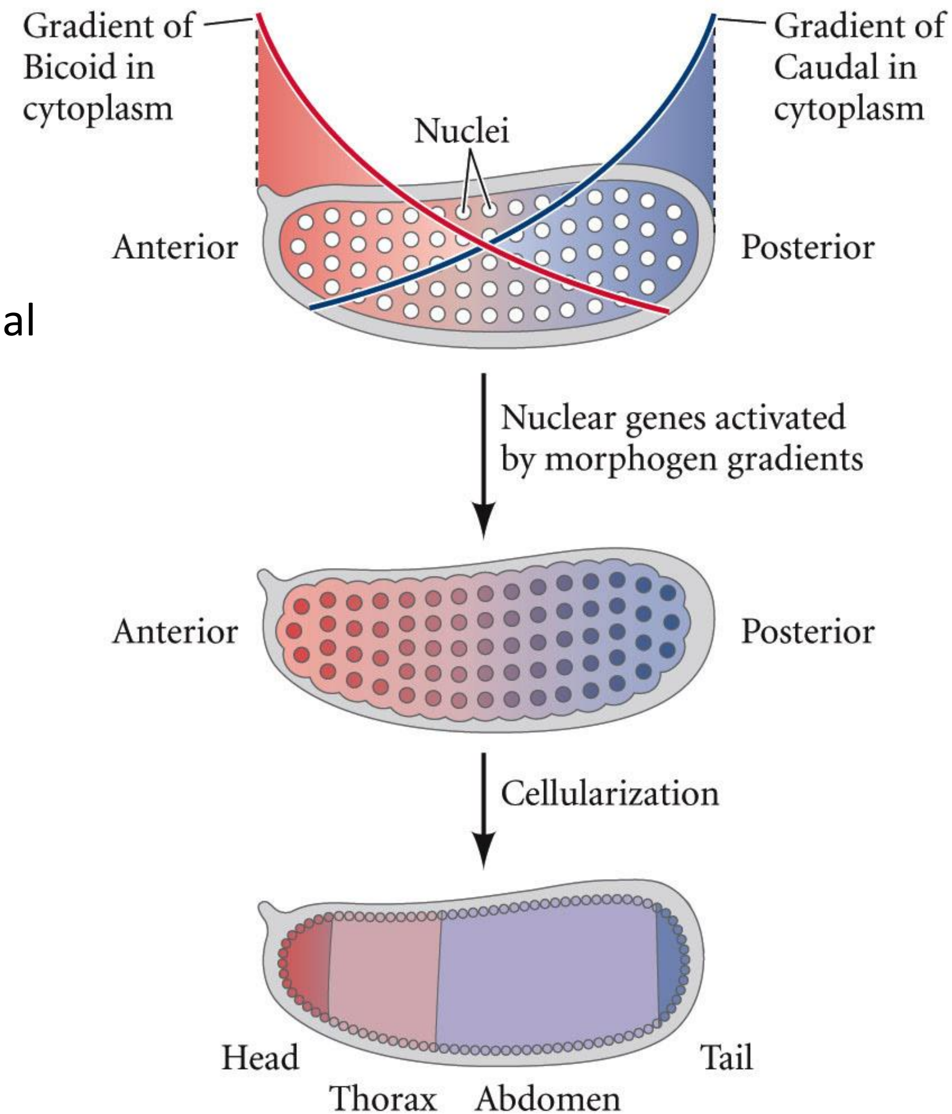
Pattern sharpening by two diffusible molecules -> inhibition



Induction

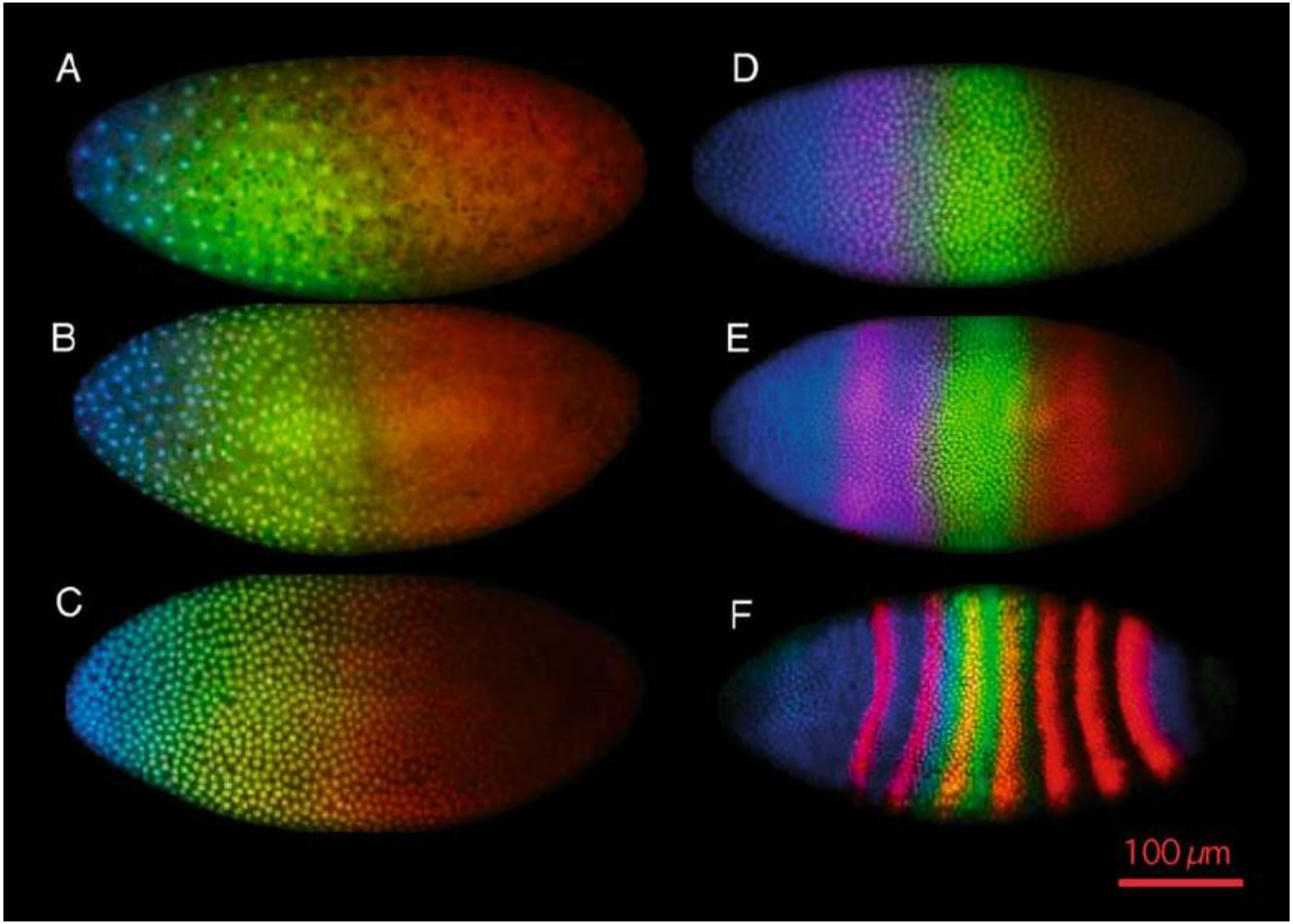
Particular case of morphogens: Syncitial specification

Bcd —| Caudal



DEVELOPMENTAL BIOLOGY, 9e, Part Figure II.10

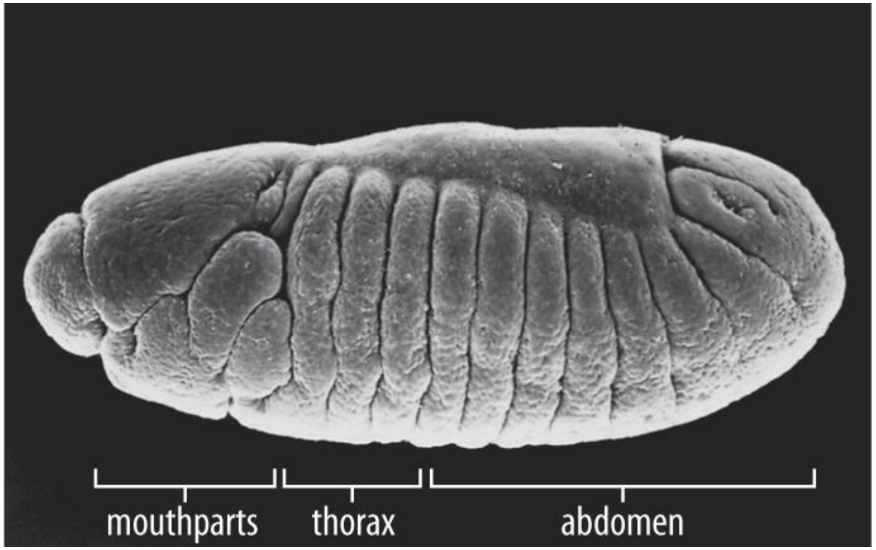
Drosophila segmentation



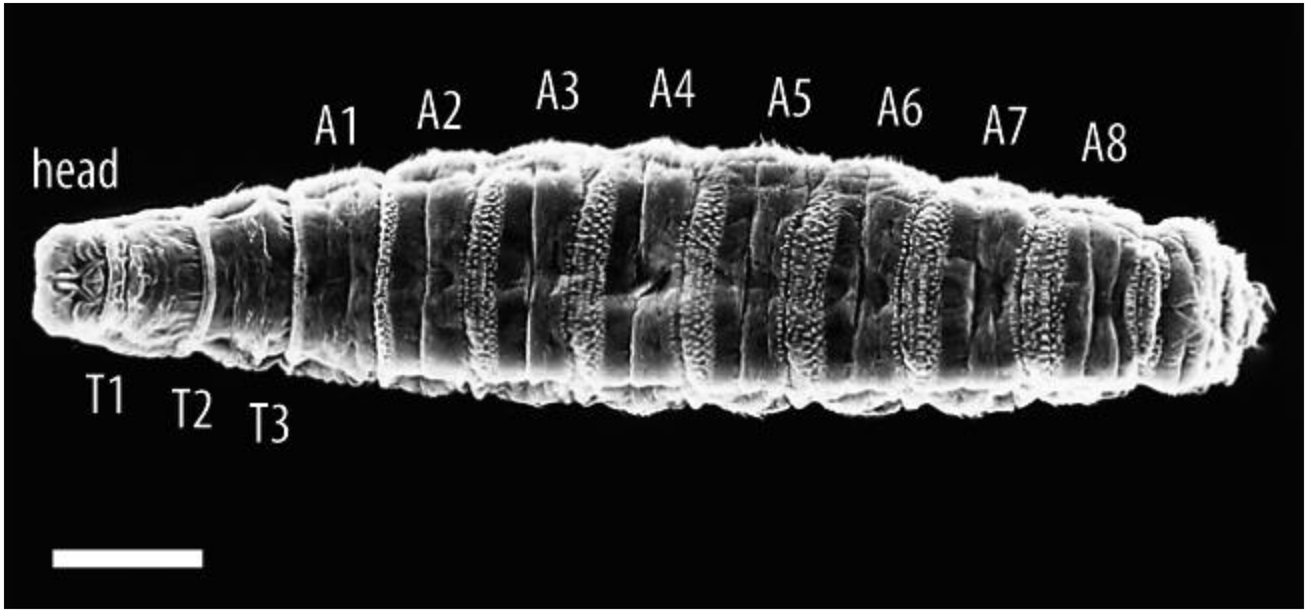
Expression patterns of gap and pair-rule genes in Drosophila embryos. A Y C : red, even-skipped; green, hunchback; blue, bicoid; D Y F : red, even-skipped; green, Kruppel; blue, hunchback. A , cycle 10; B , cycle 12, C and D , cycle 13; E , cycle 14/2; F , cycle 14/4. Anterior to the left, dorsal to the top. (Kosman et al. 1998, 1999)

Drosophila segmentation

Embryo

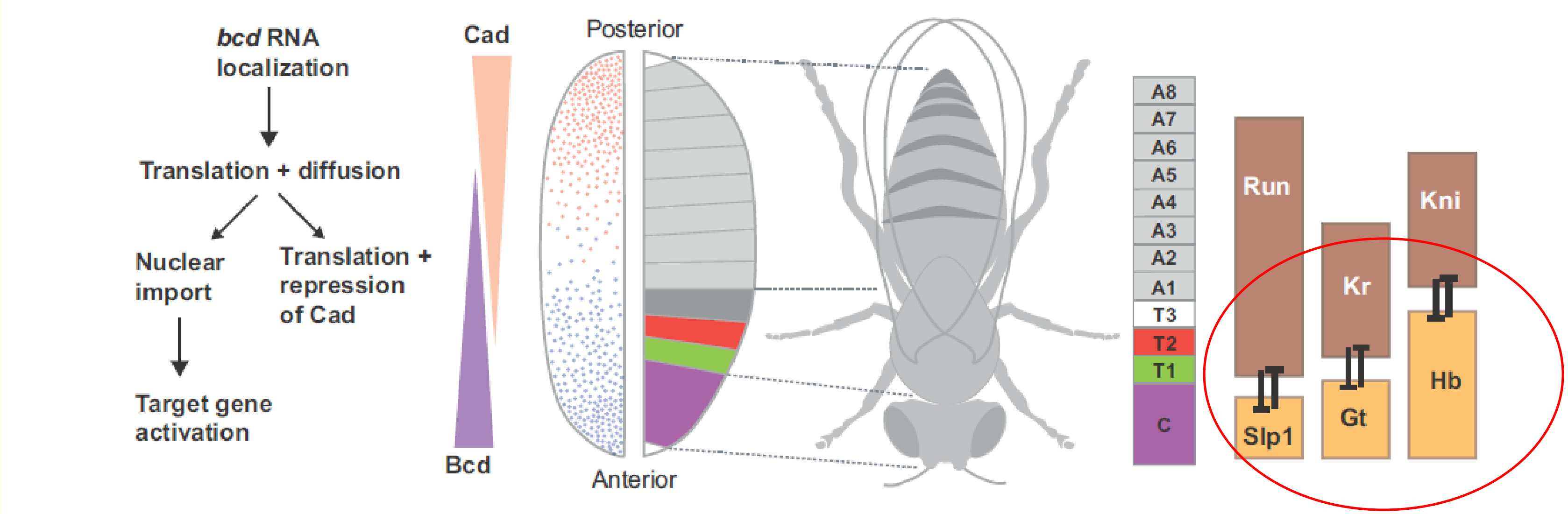


Larva



Beyond simple morphogen gradients:
Patterns refinement by diffusible inhibitors
Pattern sharpening by mutual inhibition

Box 1. Anterior-posterior (AP) patterning of the *Drosophila* blastoderm



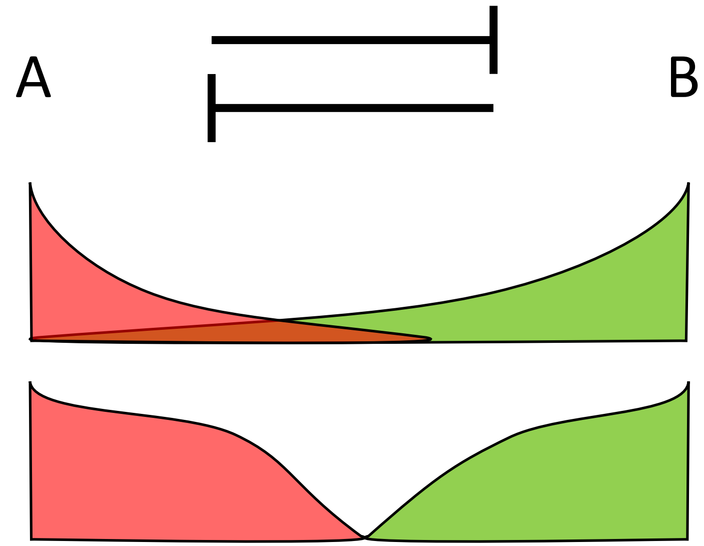
 | Development (2015) 142, 3996-4009 doi:10.1242/dev.129452

REVIEW

Morphogen rules: design principles of gradient-mediated embryo patterning

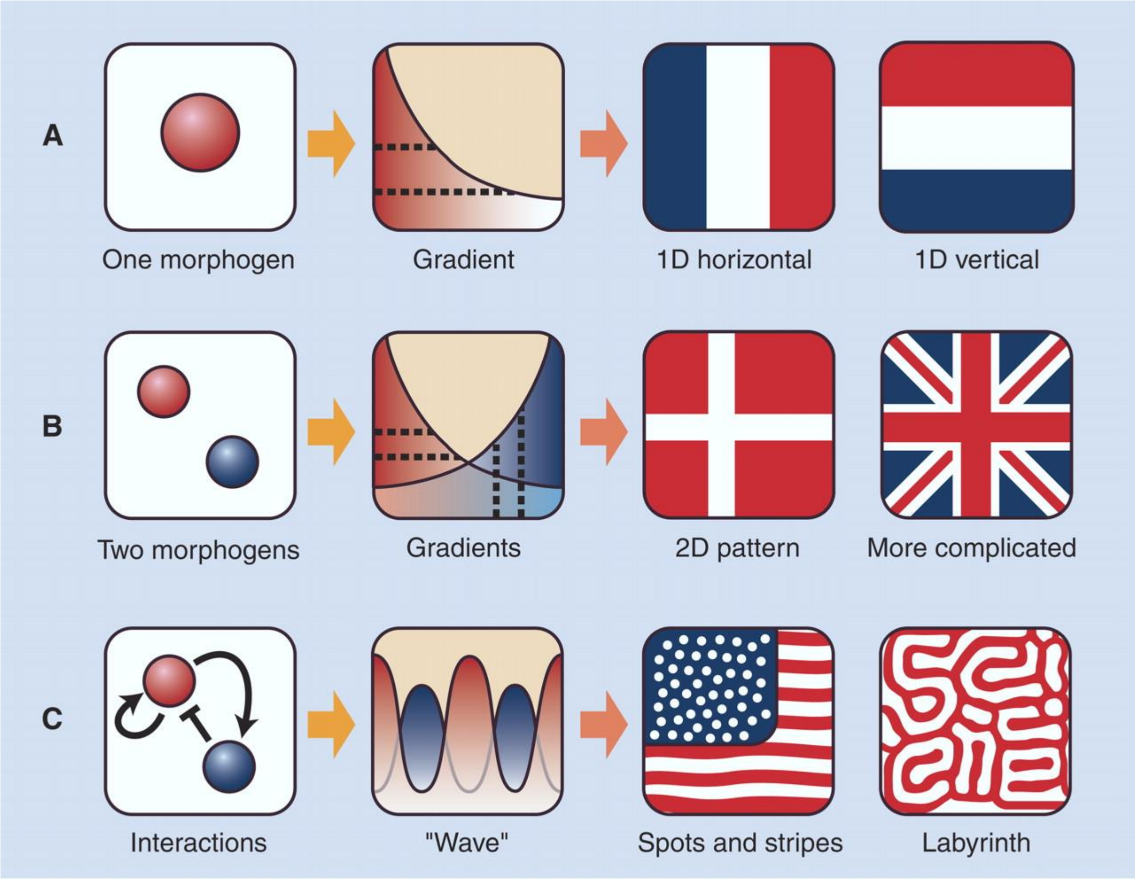
James Briscoe[1,*] and Stephen Small[2,*]

Beyond simple morphogen gradients:
Patterns refinement by diffusible inhibitors
Pattern sharpening by mutual inhibition



Induction

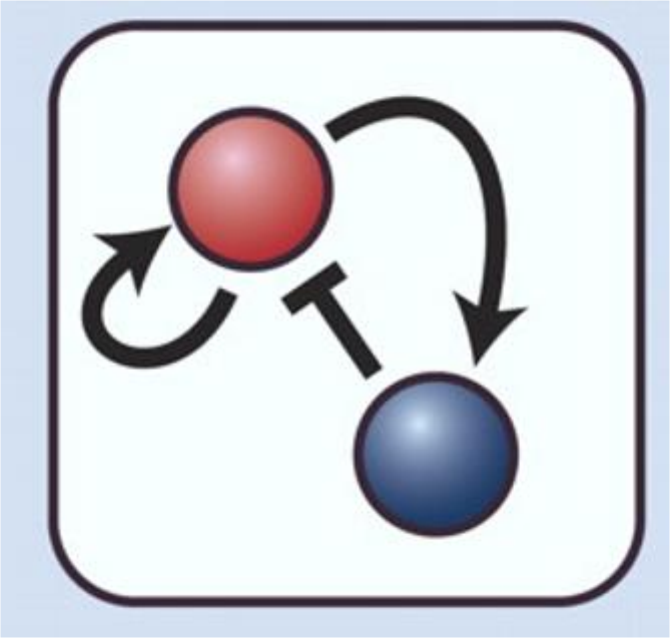
Fig. 1 Schematic drawing showing the difference between the morphogen gradient model and Turing model.



Shigeru Kondo, and Takashi Miura Science 2010;329:1616-1620

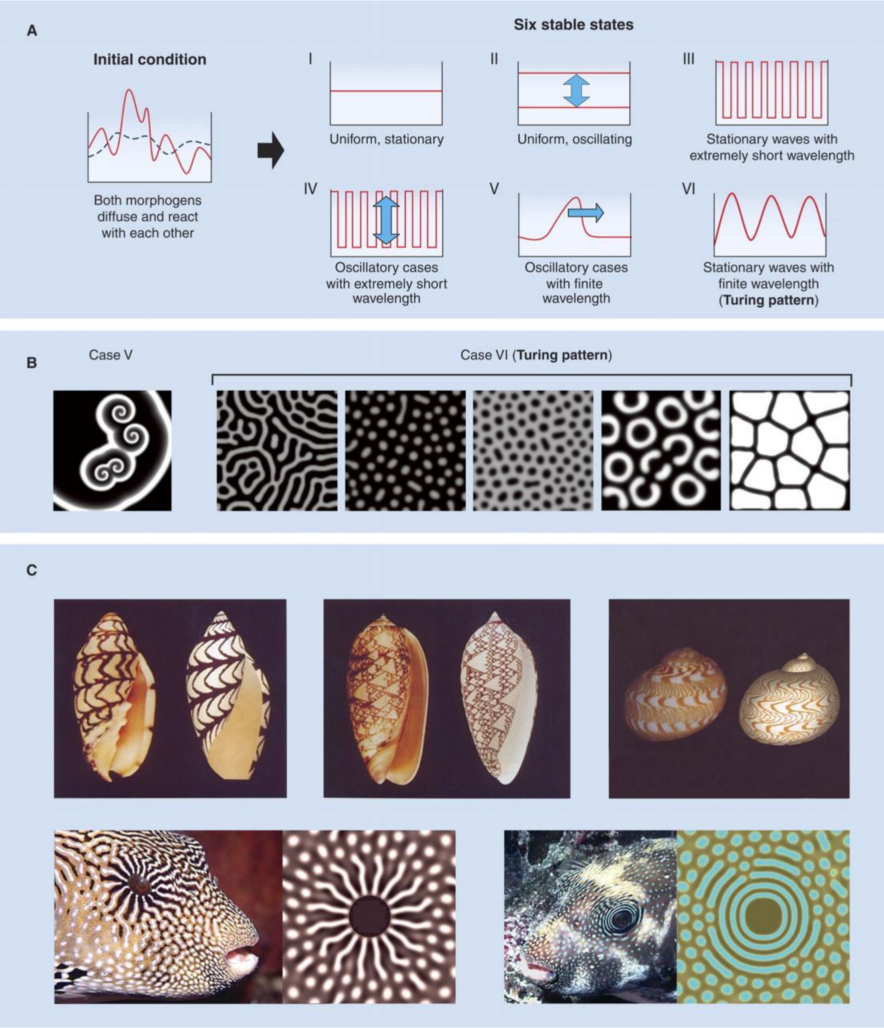
Published by AAAS

Turing model



Induction

Fig. 2 Schematic drawing showing the mathematical analysis of the RD system and the patterns generated by the simulation.



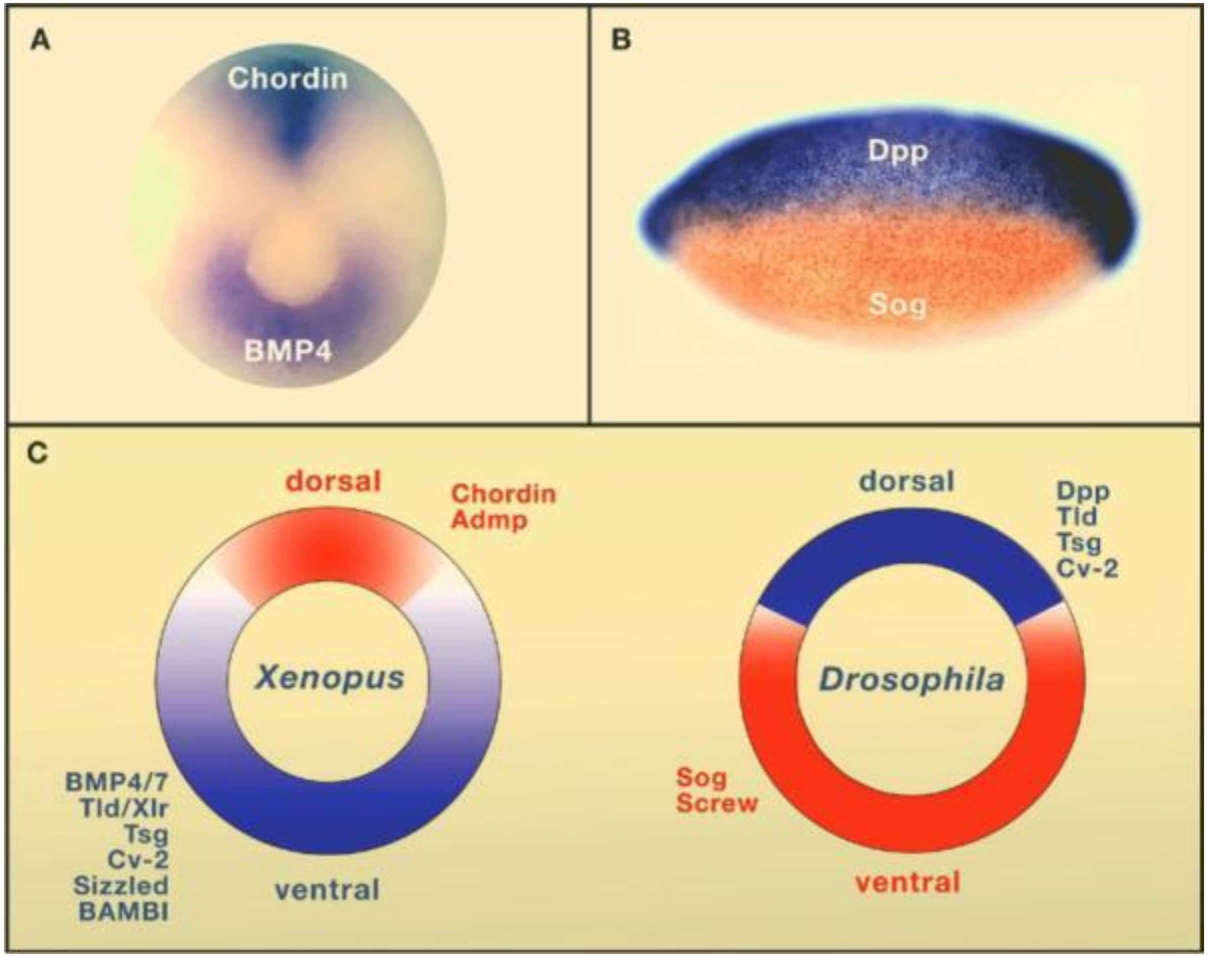
Shigeru Kondo, and Takashi Miura Science 2010;329:1616-1620

Published by AAAS

Induction

Example of establishment of a morphogen gradient

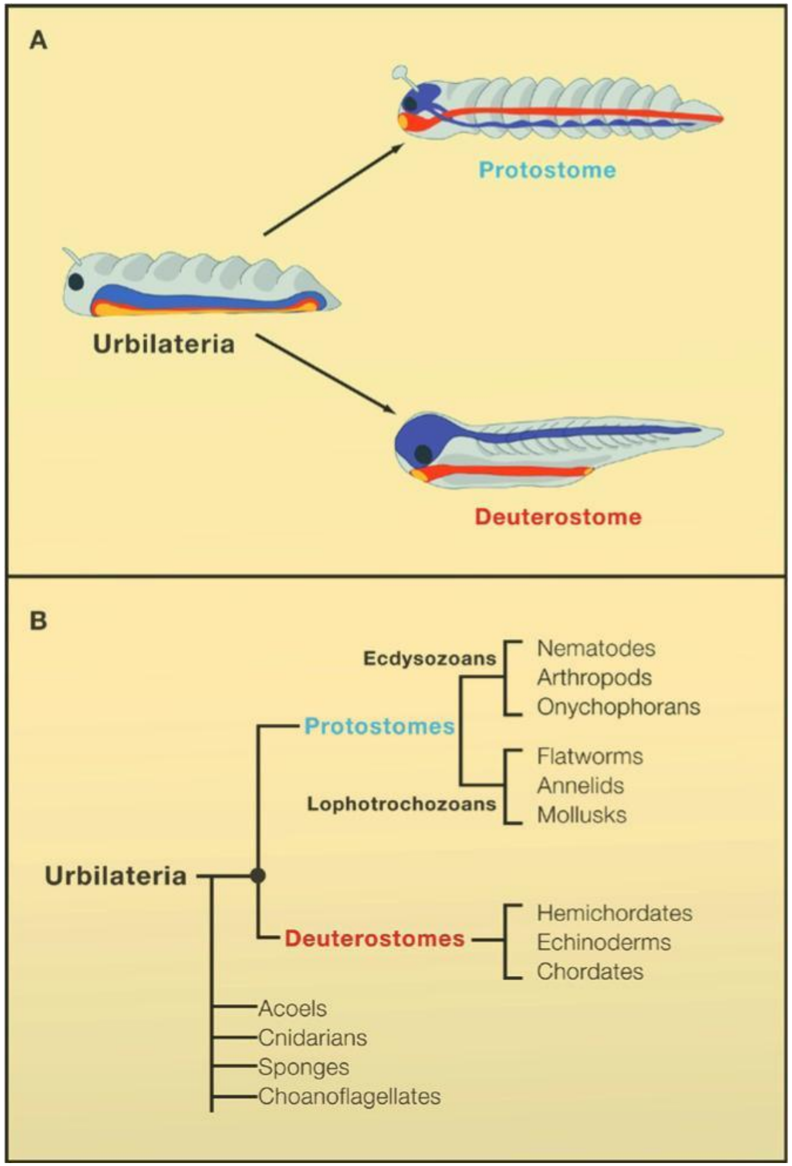
BMP signaling: BMPs, Chordin in amphibians (and other vertebrates) and flies



Vertebrate new inhibitors:

Noggin
Cerberus
Frzbs
……

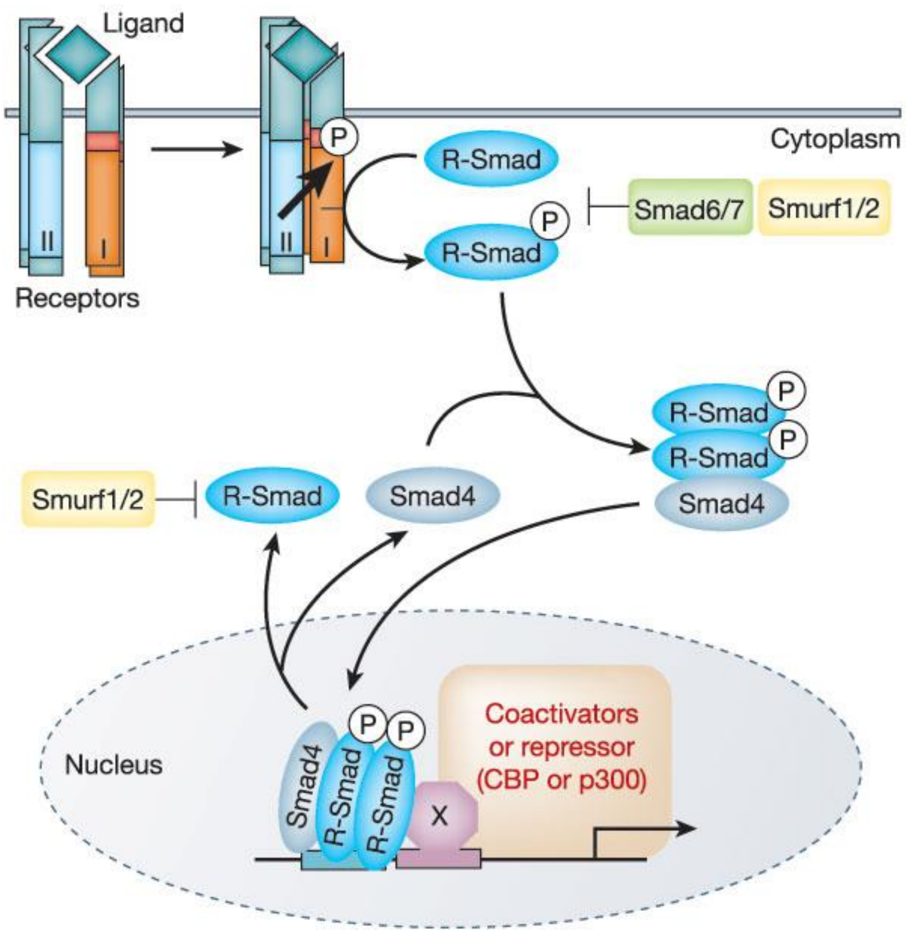
BMPs, chordin and evolution: Dorsal/Ventral inversion



Induction

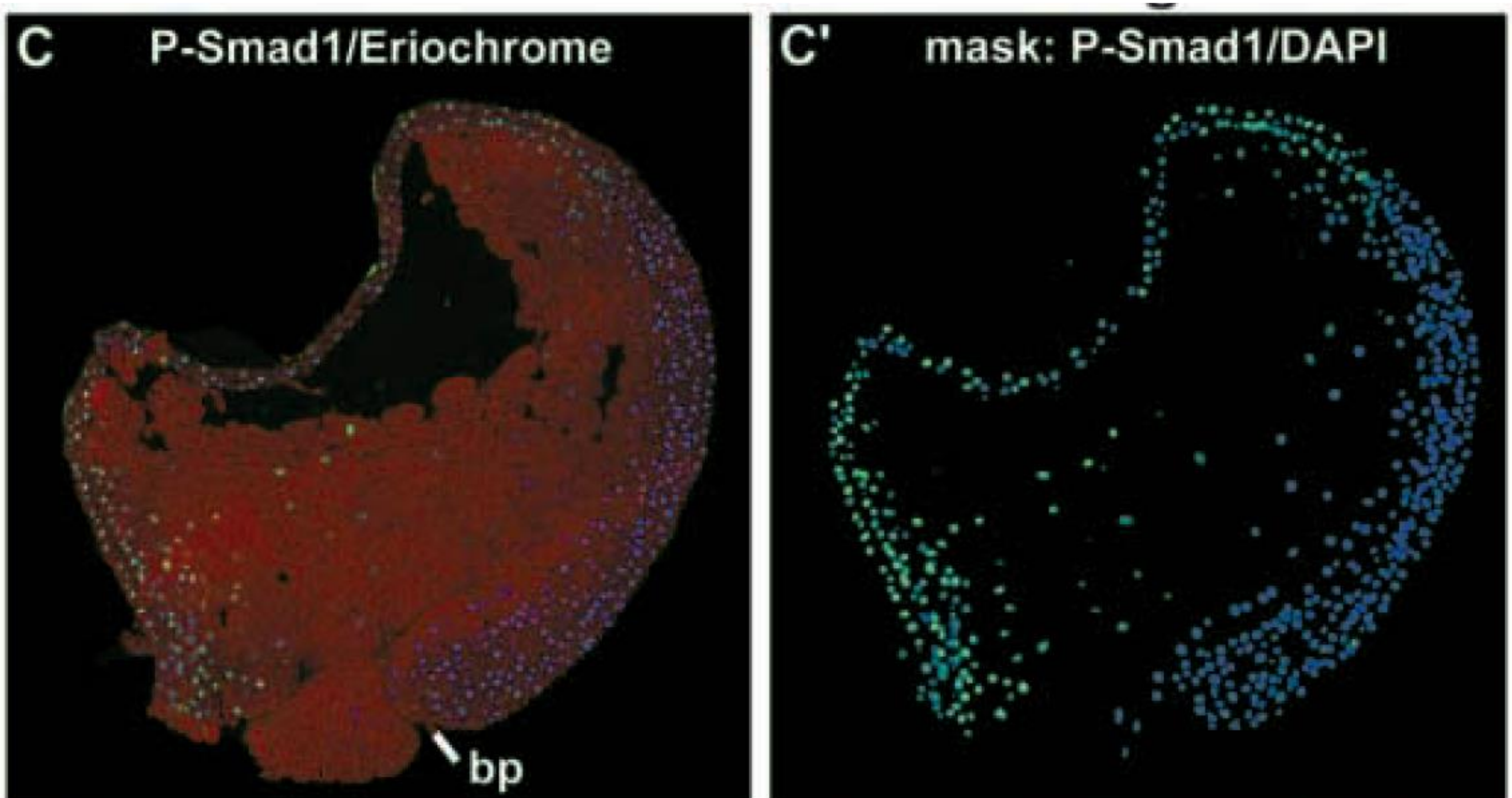
Example of establishment of a morphogen gradient

BMP signaling



Localization of BMP signaling:
Smad1 signaling during early *Xenopus* development

Analysis of nuclear P-Smad1



Green = P-Smad1
Blue = DAPI (Nuclear)
Red = Yolk

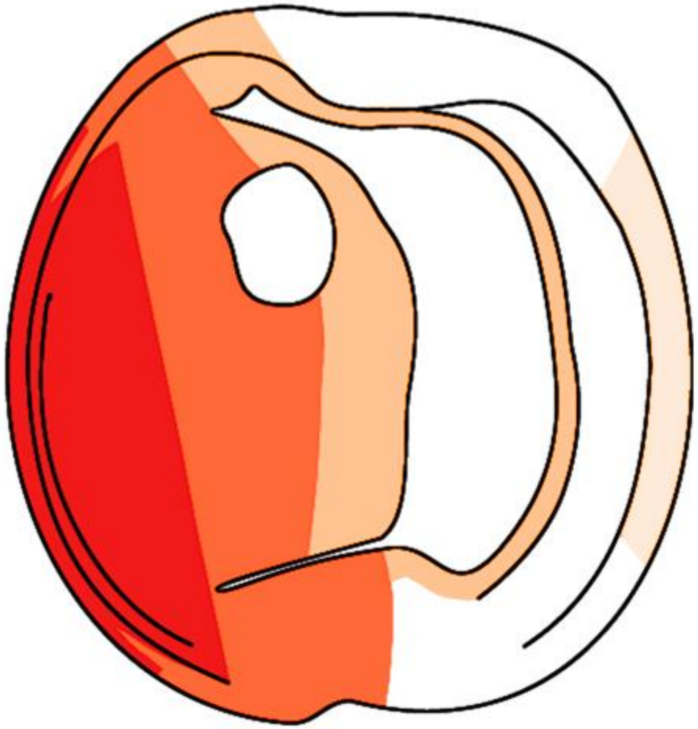
Development 129, 37-52 (2002)
Printed in Great Britain © The Company of Biologists Limited 2002
DEV2792

β-catenin, MAPK and Smad signaling during early *Xenopus* development

Anne Schohl and François Fagotto*

Department of Cell Biology, Max Planck Institute for Developmental Biology, Spemannstrasse 35, D-72076 Tübingen, Germany
*Author for correspondence (e-mail: francois.fagotto@tuebingen.mpg.de)

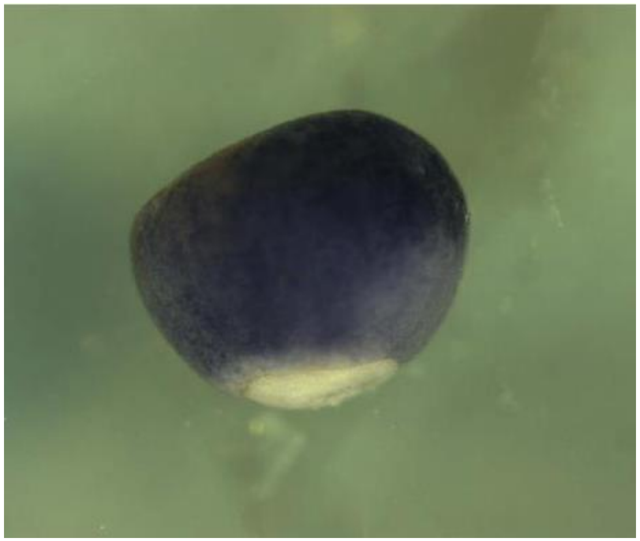
st16



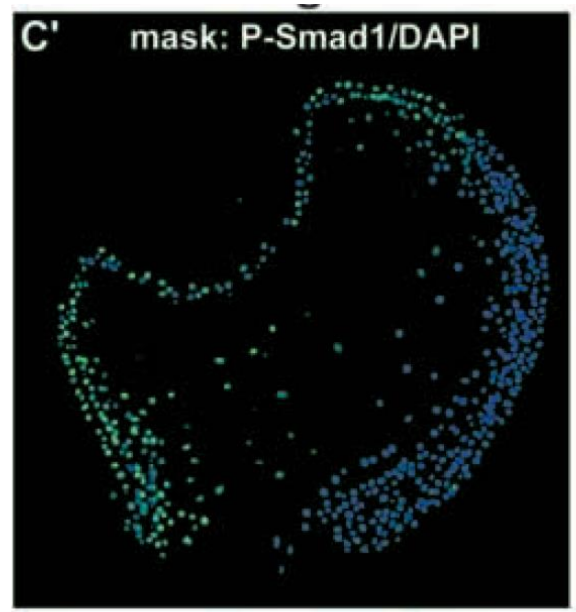
Induction

Example of establishment of a morphogen gradient

In situ hybridization zygotic BMP

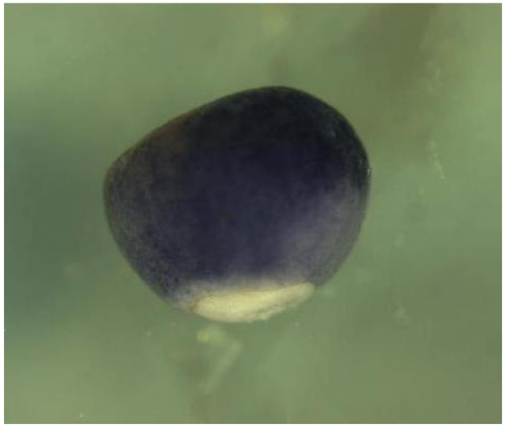


?



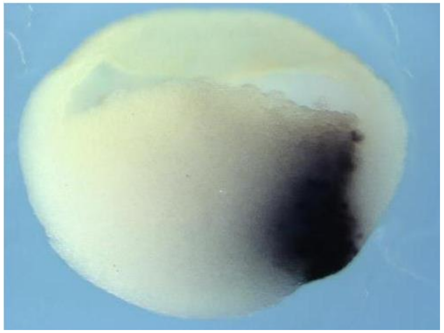
Establishment and sharpening of the dorso-ventral Smad activation pattern

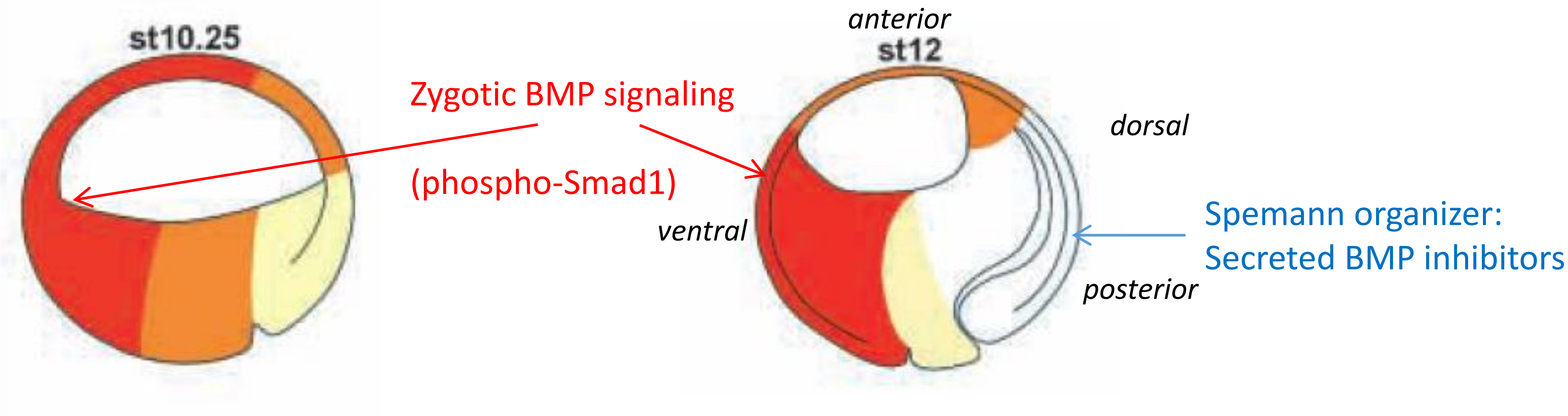
In situ hybridization zygotic BMP pathway and inhibitors



BMP4

Chordin





Diagrams adapted from:
Schohl and Fagotto, 2002, β-catenin, MAPK and Smad signaling during early Xenopus development. Development 129, 37-52

Example of establishment of a morphogen gradient
BMP signaling

BMP = TGFβ family

Chordin = BMP inhibitor

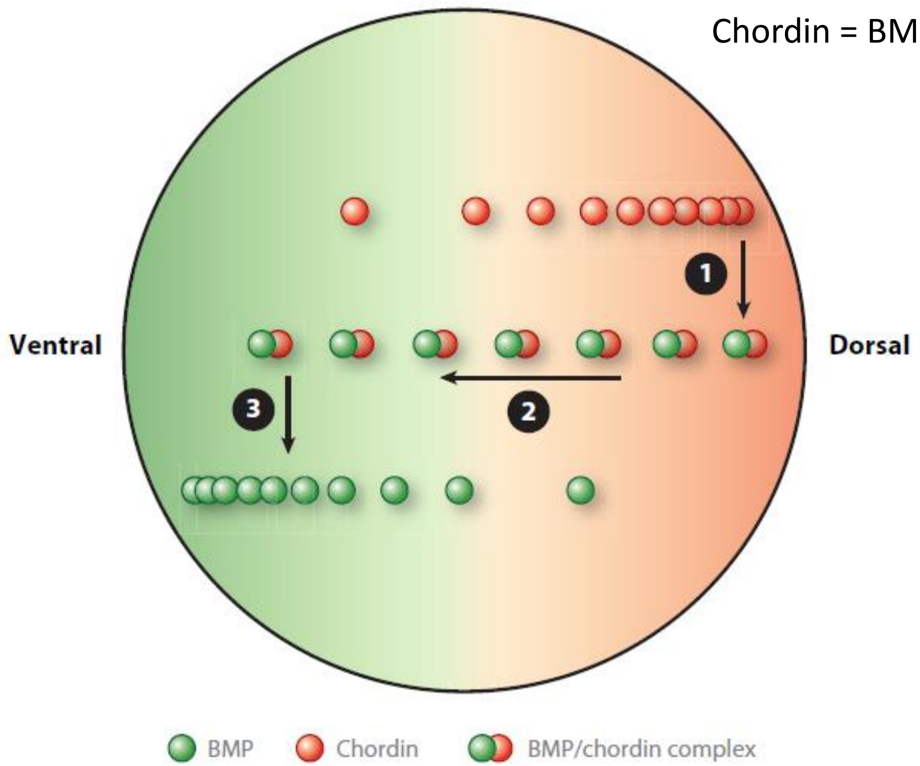
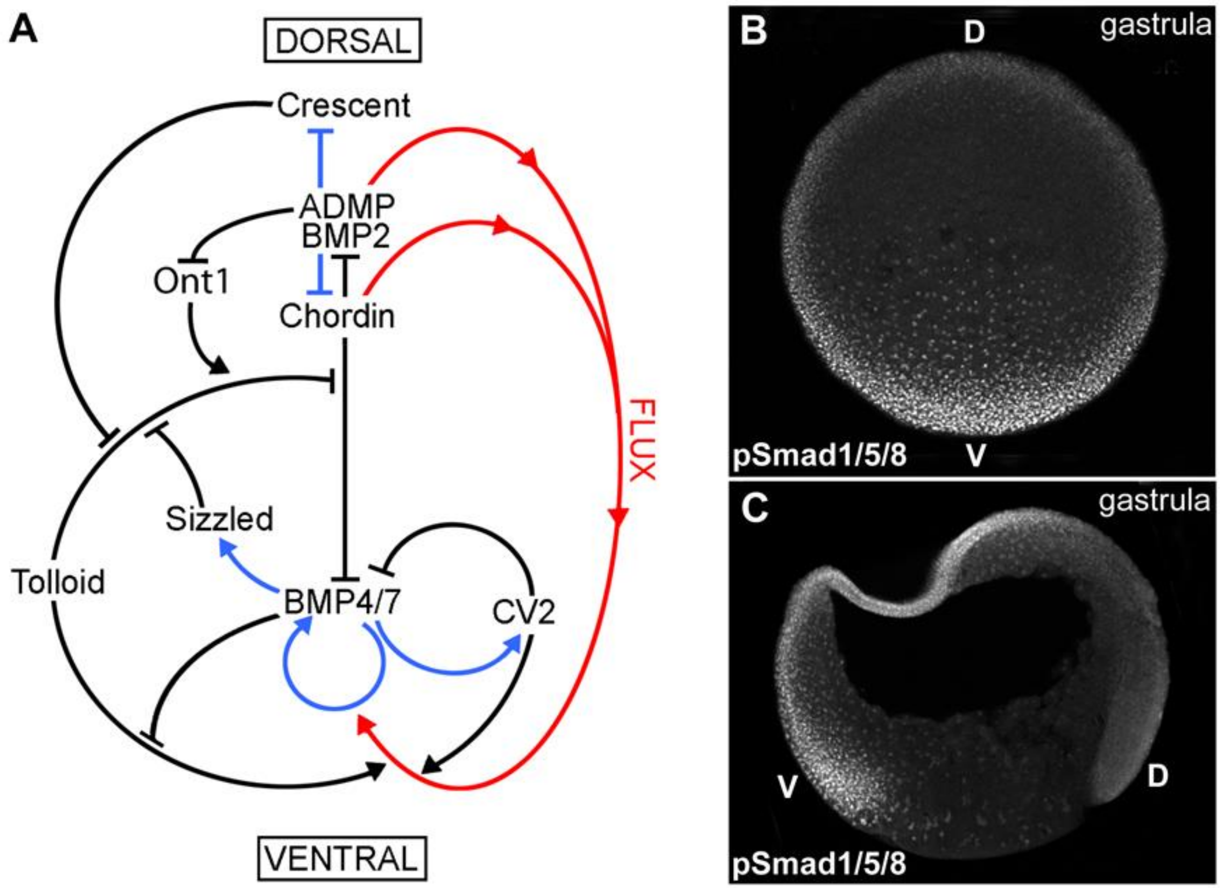


Figure 2
The bone morphogenetic protein (BMP) shuttling mechanism. In *Xenopus* embryos, Chordin (*red*) is secreted from the dorsal region, whereas BMP (*green*) is initially uniformly expressed. Chordin, upon secretion from the dorsal region, forms a complex with and antagonizes BMP (1). This interaction mobilizes BMP as complexes diffuse in the extracellular space (2). Chordin is cleaved by an extracellular protease, which causes it to release and deposit BMP at the site of cleavage (3). This shuttling generates a ventral-to-dorsal gradient. Figure based on Lewis (2008).

Induction

Example of establishment of a morphogen gradient BMP signaling



Xenopus embryo

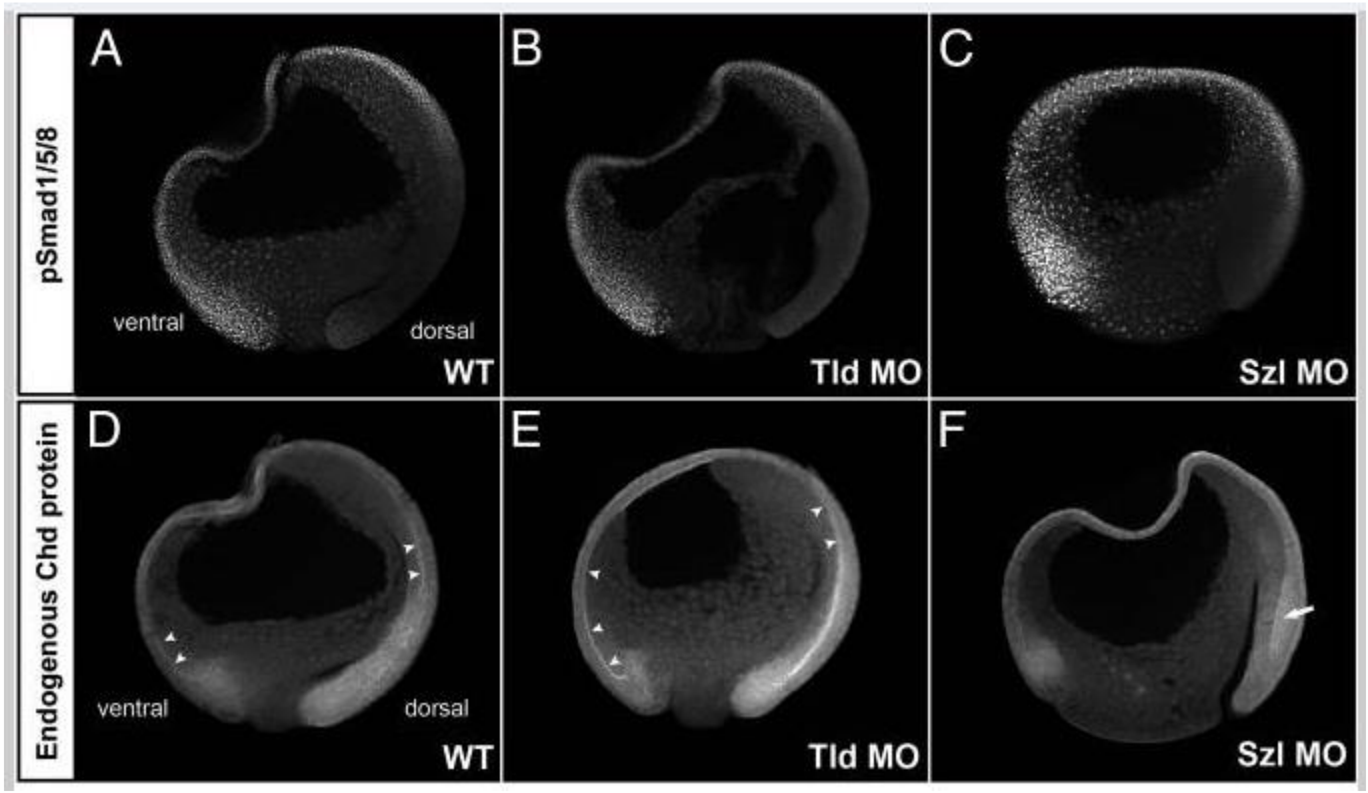
Proc Natl Acad Sci U S A. 2013 Dec 17;110(51):20372-9. doi: 10.1073/pnas.1319745110. Epub 2013 Nov 27.

Chordin forms a self-organizing morphogen gradient in the extracellular space between ectoderm and mesoderm in the Xenopus embryo.

Plouhinec JL[1], Zakin L, Moriyama Y, De Robertis EM.

Example of establishment of a morphogen gradient
BMP signaling

Importance of inhibitory feedback loops for proper gradient shaping

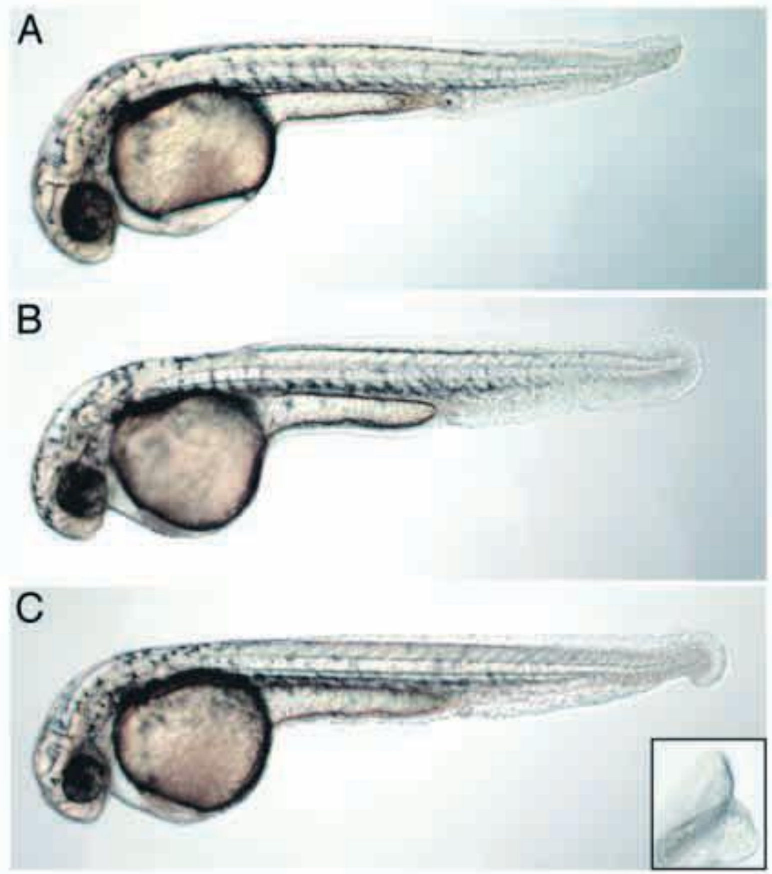


Proc Natl Acad Sci U S A. 2013 Dec 17;110(51):20372-9. doi: 10.1073/pnas.1319745110. Epub 2013 Nov 27.

Chordin forms a self-organizing morphogen gradient in the extracellular space between ectoderm and mesoderm in the Xenopus embryo.

Plouhinec JL[1], Zakin L, Moriyama Y, De Robertis EM.

Limitations of genetics to study cellular/molecular mechanisms in vertebrates
The example of tolloid in Zebrafish



Tetraploid!!
+ Compensation??

Fig. 1. Injection of *tld* mRNA rescues the *mfn* mutant phenotype. (A) An uninjected *mfn* mutant embryo displays a partial loss of the ventral tail fin. Embryos injected with *tld* mRNA can be rescued to wild-type (B) or a weakly ventralized phenotype (C) as indicated by a duplicated ventral tail fin tip (inset, posterior view). The phenotype in C is also observed in wild-type embryos ventralized by overexpression of *tld* (data not shown).

Development 126, 3119-3130 (1999)
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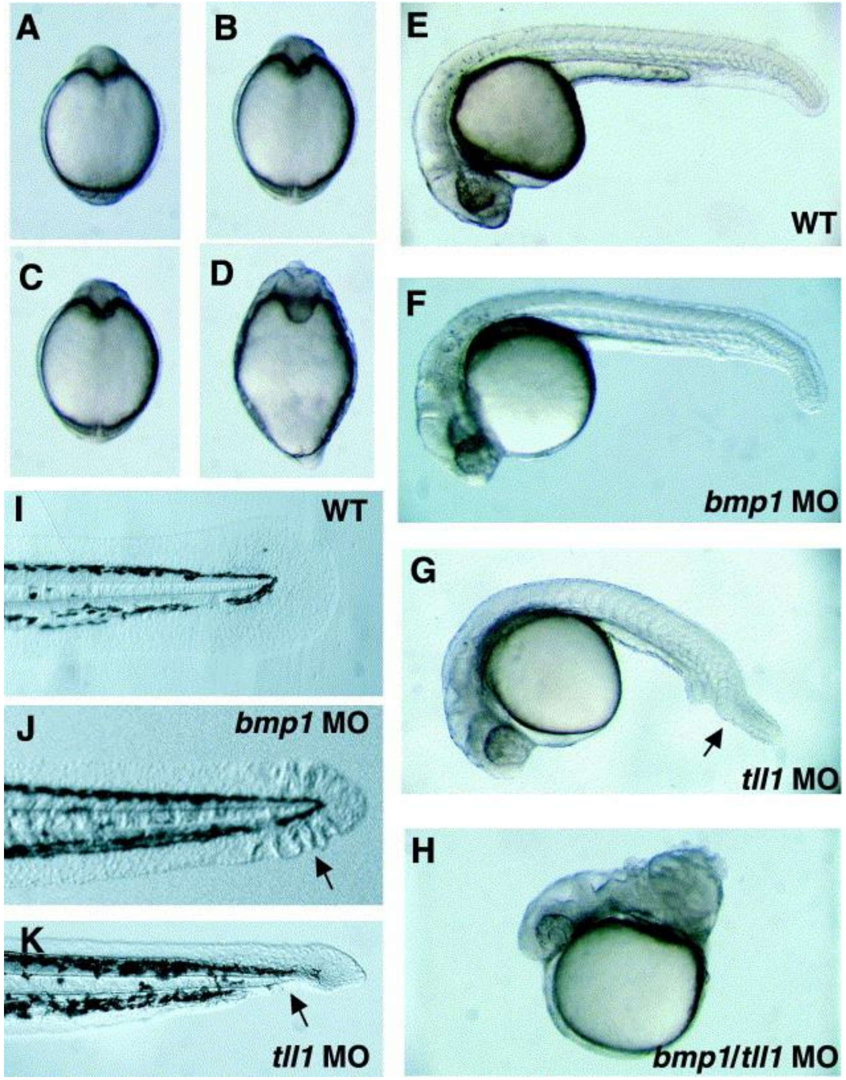
DEV3013 31

The role of *tolloid/mini fin* in dorsoventral pattern formation of the zebrafish embryo

Stephanie A. Connors[1], Jamie Trout[1], Marc Ekker[2] and Mary C. Mullins[1,*]

bmp1 and *mini fin* are functionally redundant in regulating formation of the zebrafish dorsoventral axis

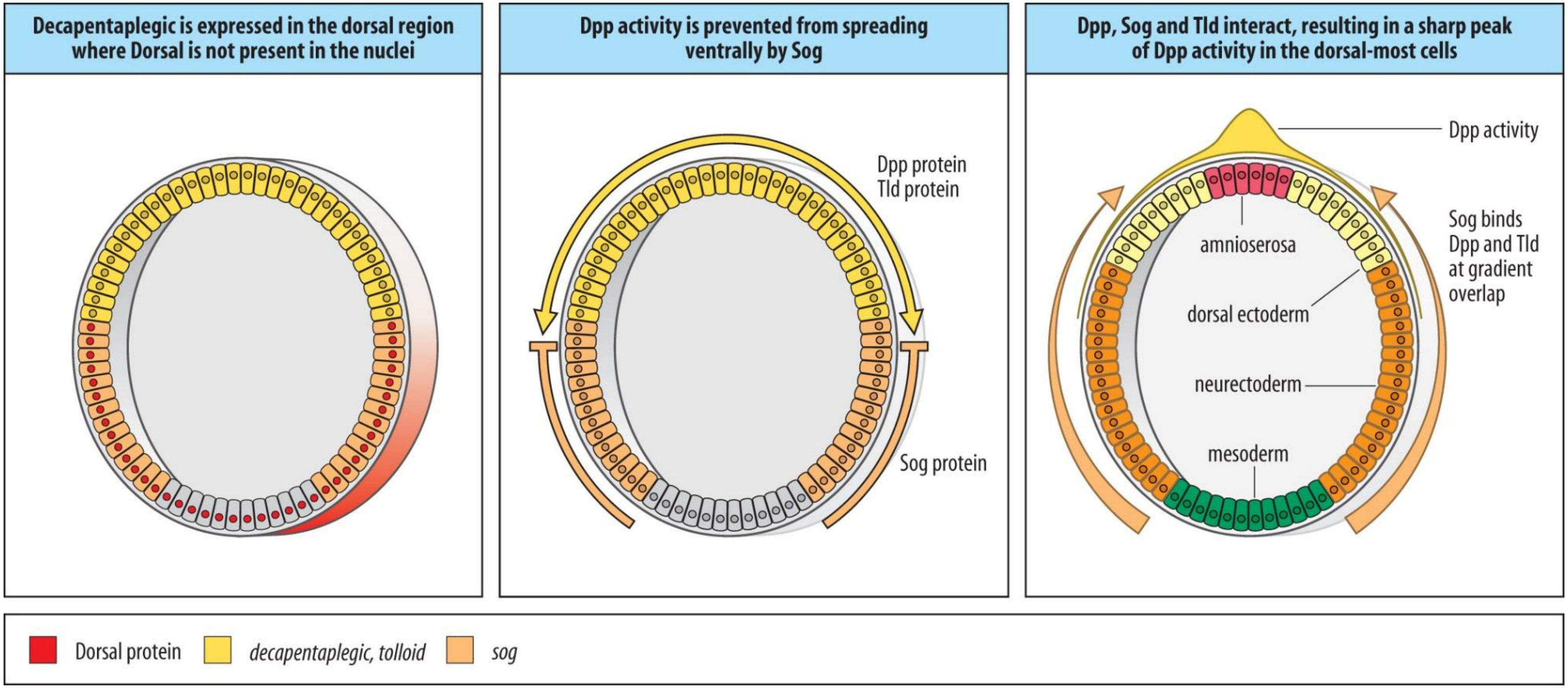
Reema Jasuja [a], Nikolas Voss [b], Gaoxiang Ge [c], Guy G. Hoffman [c], Jamie Lyman-Gingerich [b], Francisco Pelegri [b], Daniel S. Greenspan [a,c,d,*]



Induction

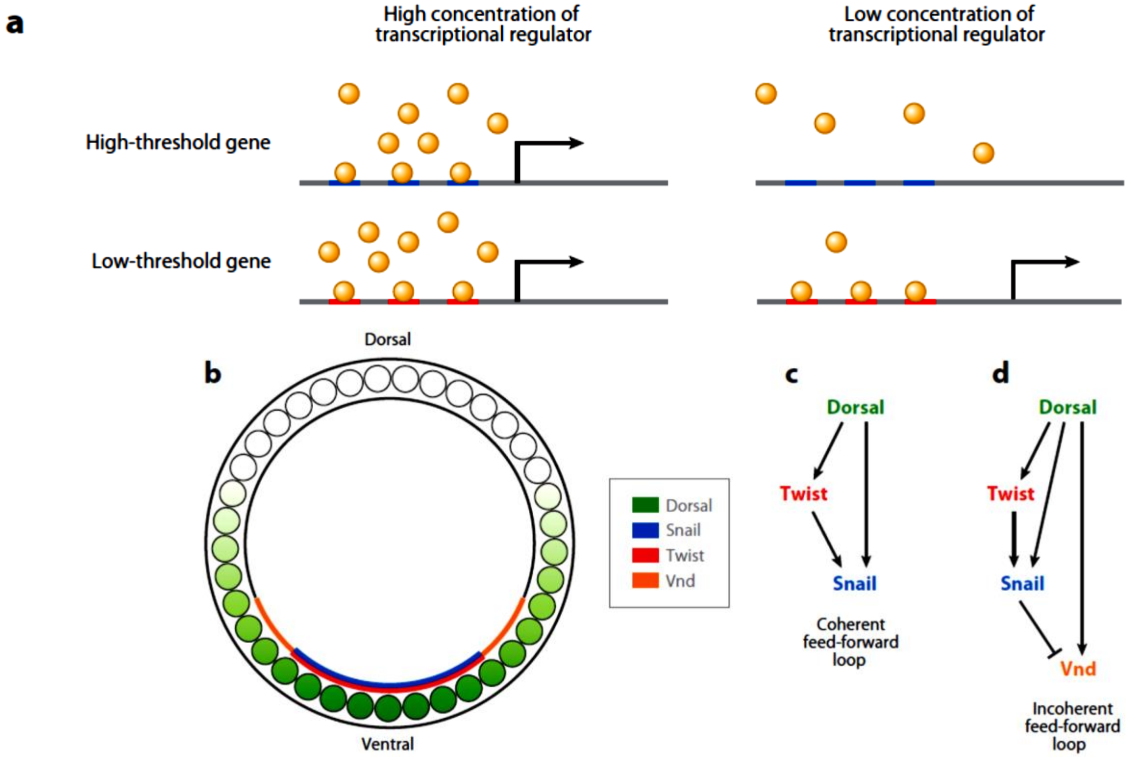
Example of establishment of a morphogen gradient
Dorsal ventral patterning in Drosophila

Dpp = BMP, Sog = Chordin, Tld = tolloid = protease that cleaves Sog



Induction

Example of establishment of a morphogen gradient
Dorsal ventral patterning in Drosophila

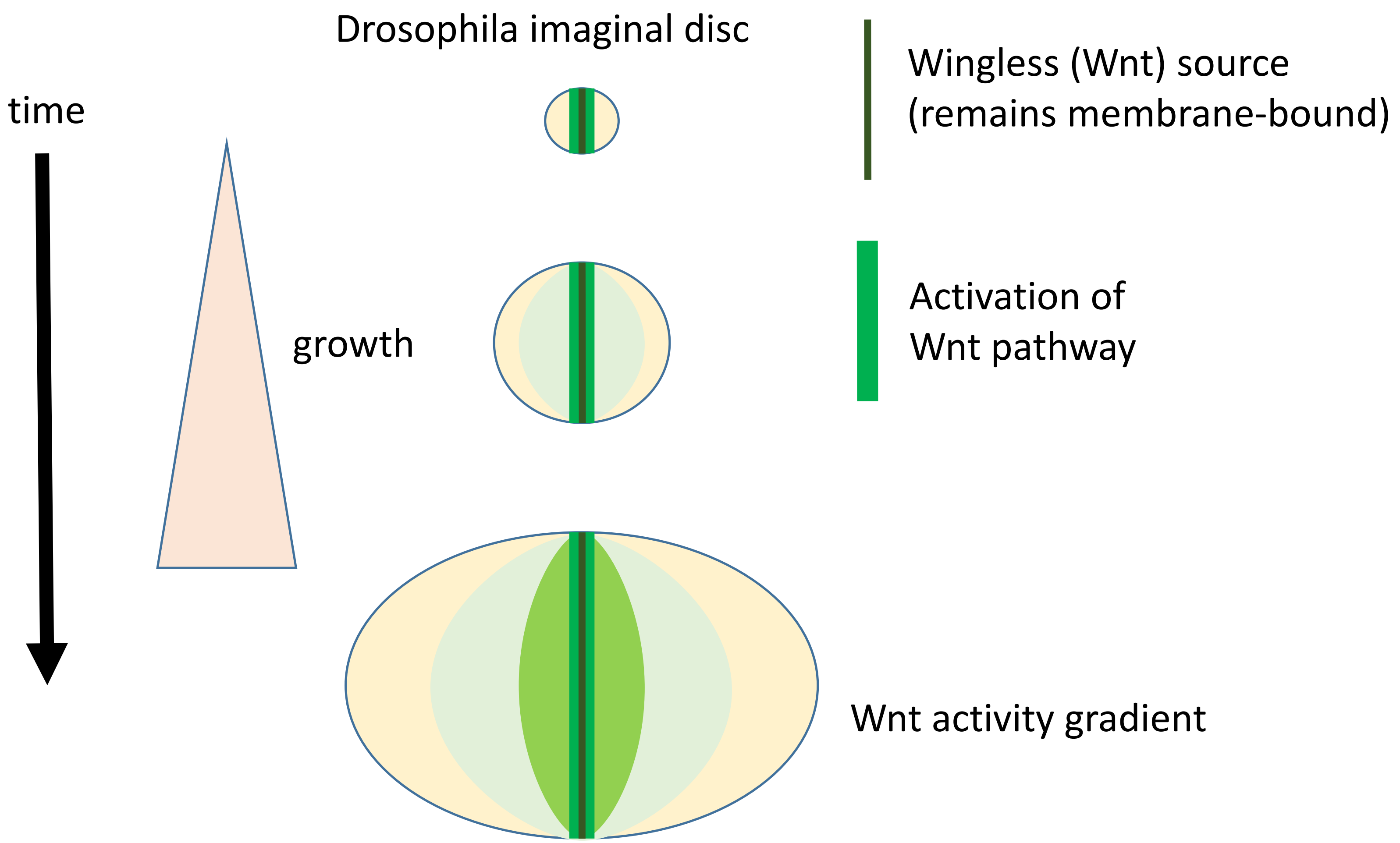


Vnd=ventral nervous system defective

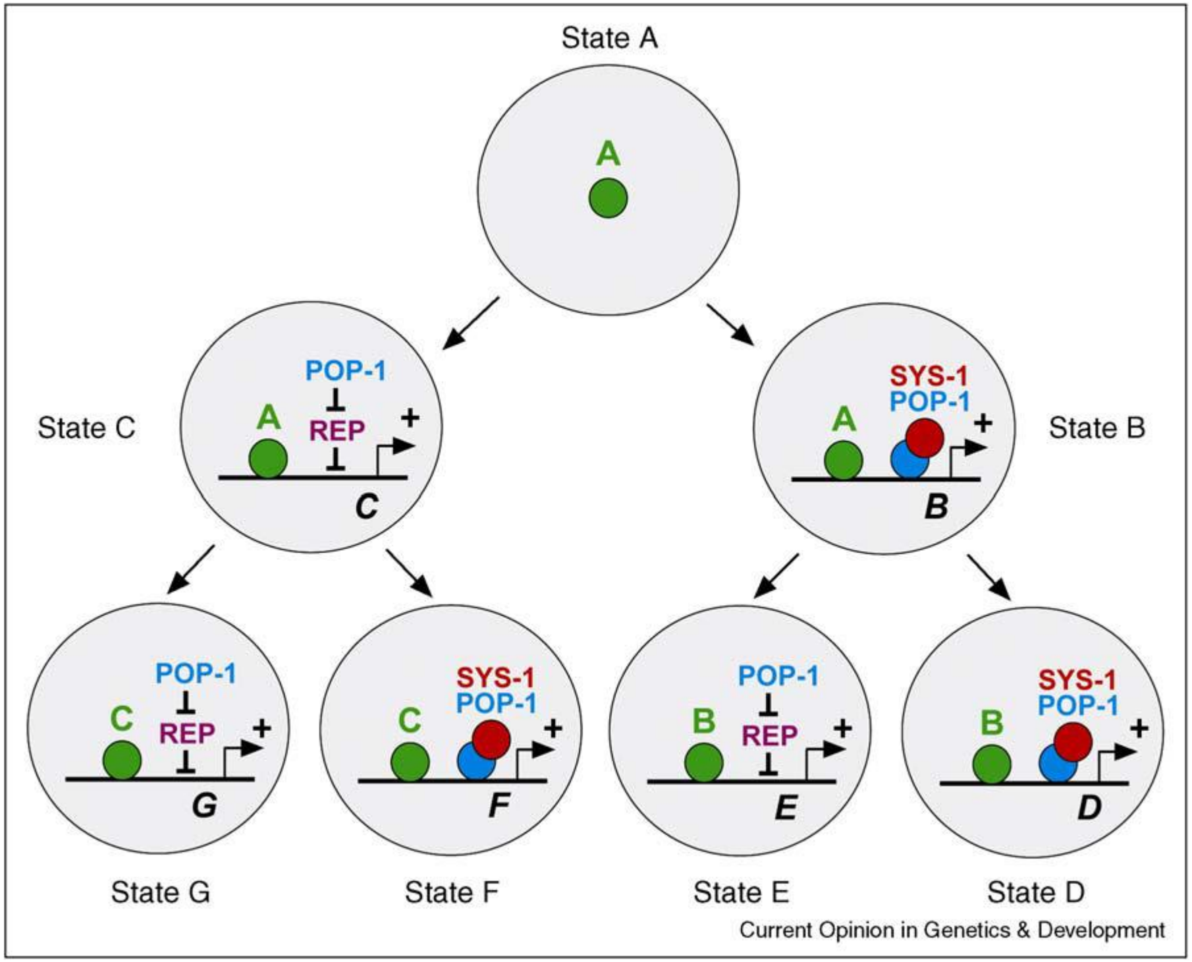
Figure 5

Gradient interpretation. (*a*) Interpretation by DNA-binding sites with varying affinity for transcriptional regulator (*gold*). The promoter of the top gene contains three low-affinity binding sites (*blue*; high-threshold gene); the promoter of the bottom gene contains three high-affinity binding sites (*red*; low-threshold gene). At high regulator concentrations, all sites in both promoters are bound, and both genes are expressed. At low concentrations, only the high-affinity sites are occupied, and only the gene with high-affinity sites is expressed. Based on Ashe & Briscoe (2006). (*b*) The ventral-to-dorsal nuclear Dorsal gradient (*green*) in *Drosophila* embryos is illustrated in a cross section. The expression domains of the Dorsal target genes Snail (*blue*), Twist (*red*), and Vnd (*orange*) are indicated. Based on Reeves & Stathopoulos (2009). (*c*) A coherent feed-forward loop initiated by Dorsal. (*d*) An incoherent feed-forward loop initiated by Dorsal. This loop restricts the expression of Vnd to the lateral regions of the embryo.

Gradient without a diffusible morphogen?



Cell fate decision: binary decisions and reuse of the same signaling pathways



Wnt pathway in C.elegans. Pop1 = TCF

Current Opinion in Genetics & Development 2010, 20:362–368

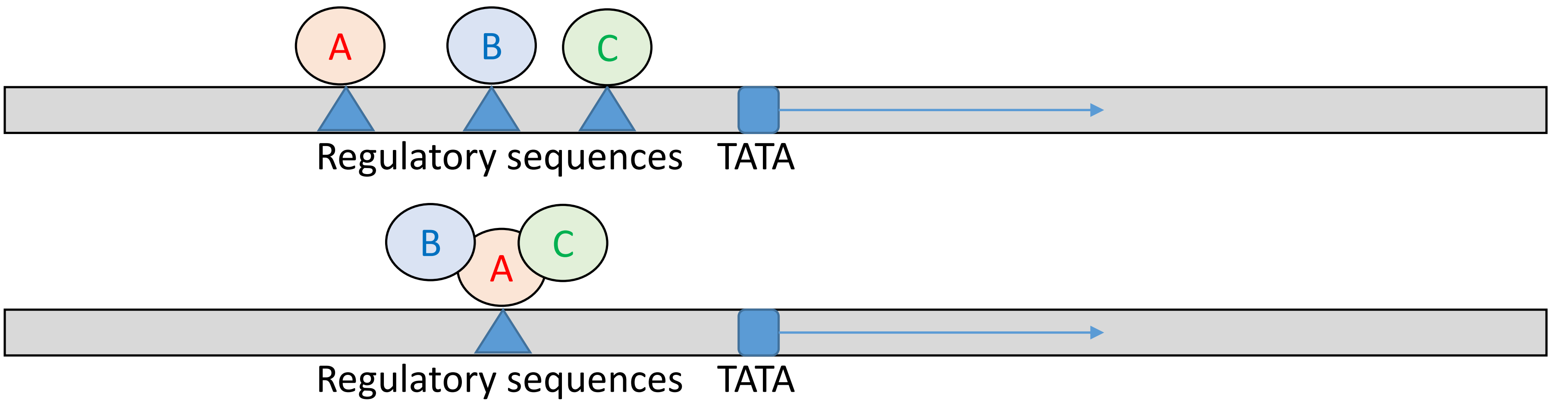
But not that ‘simple’…

Induction

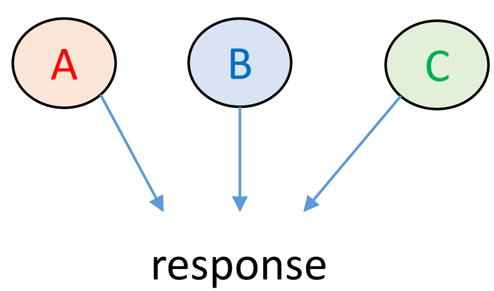
Combinatorial control + Temporal sequence

Combinatorial control

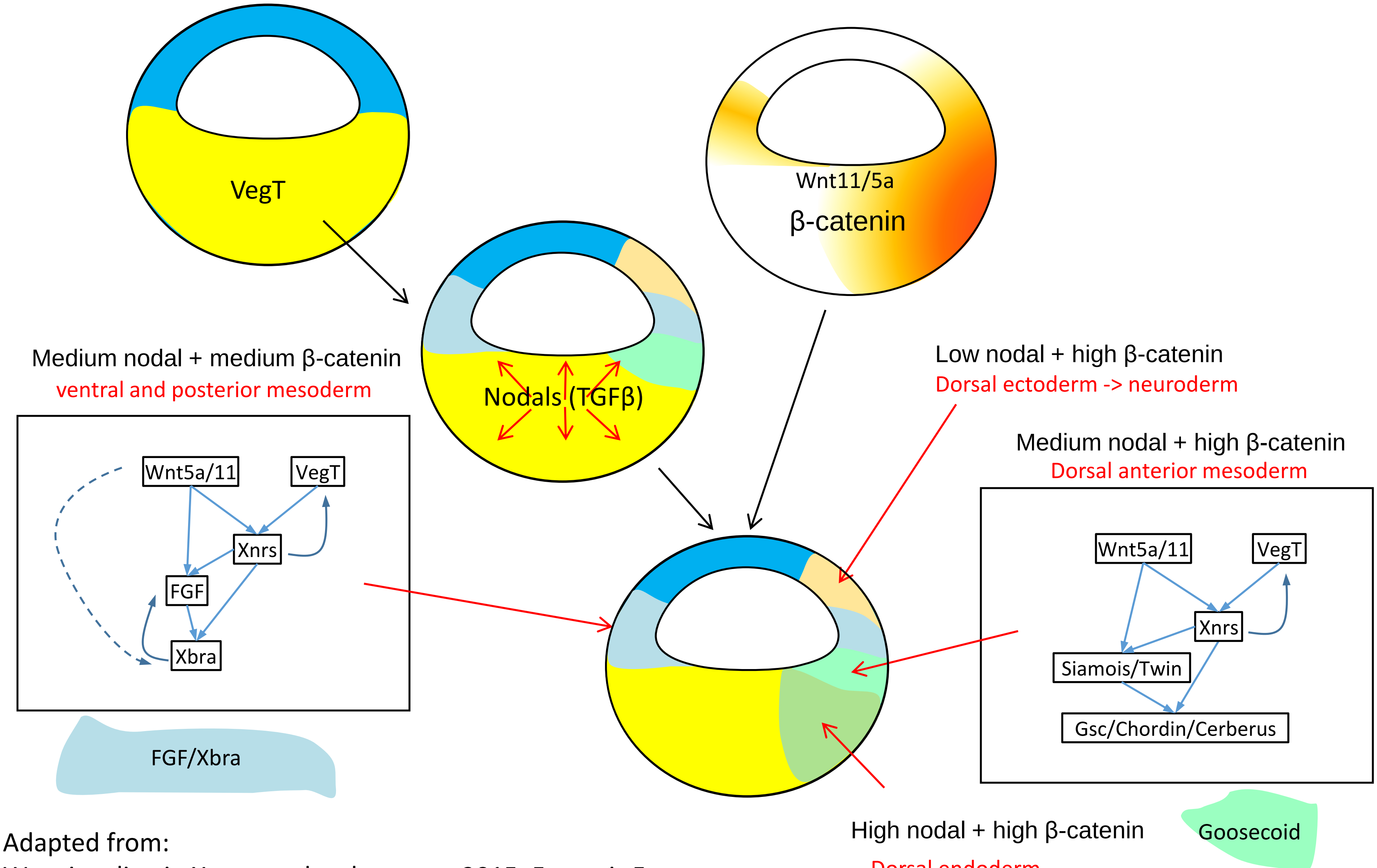
Transcriptional level:



Signal transduction level:



Establishment of the early pattern: Dosage combinations of the Wnt-β-catenin and VegT-nodal pathways

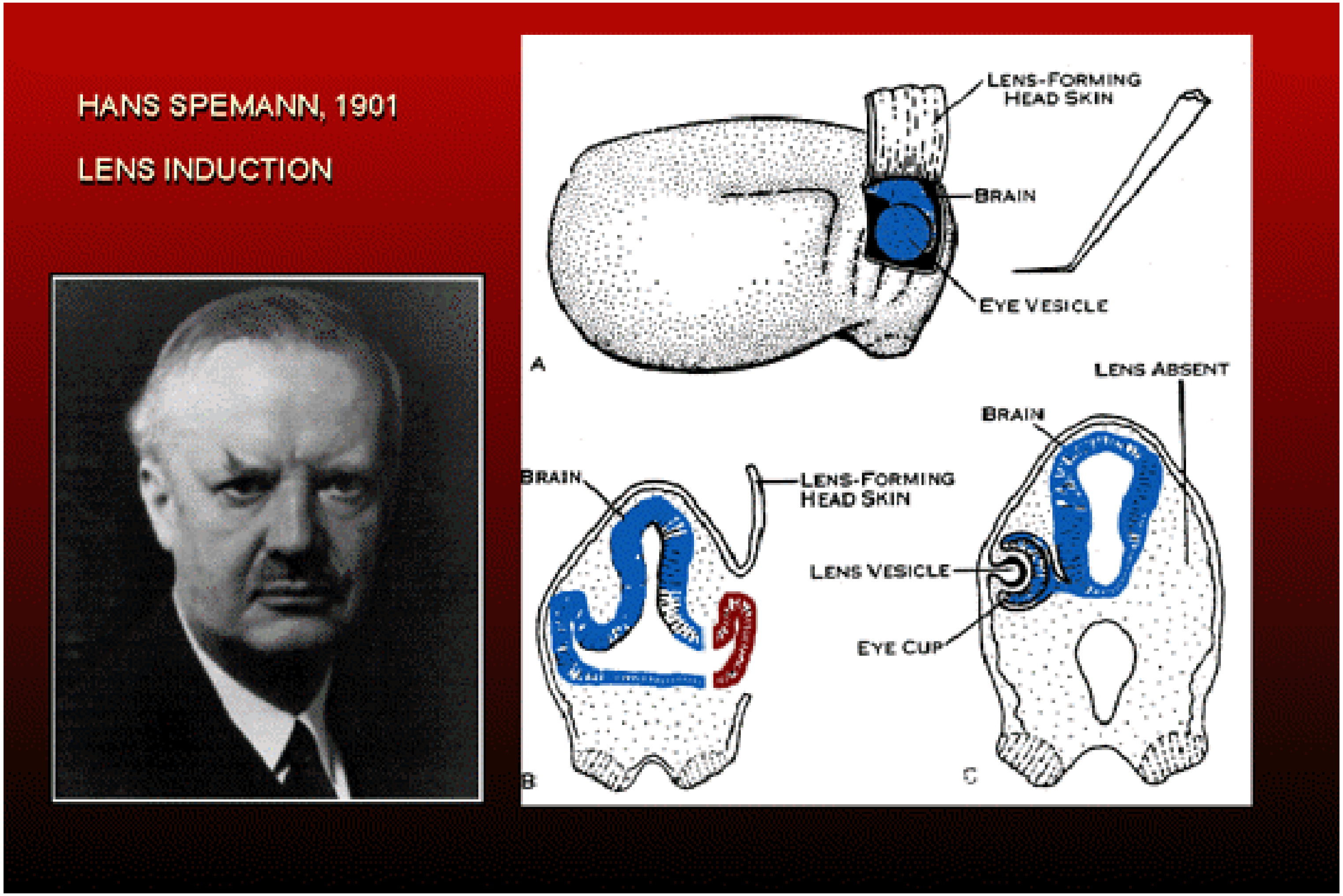


Adapted from:
Wnt signaling in Xenopus development, 2015, François Fagotto in “Xenopus Development”. ed. by M. Kloc & J. Z. Kubiak.

Introduction to cell fate and plasticity during embryonic development

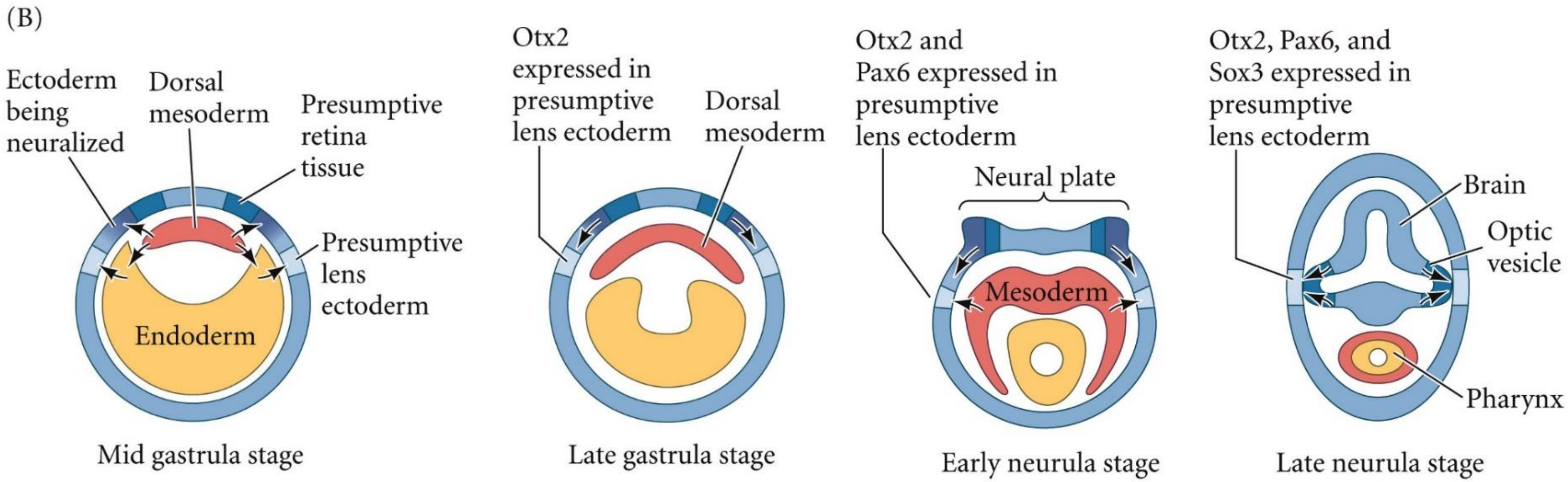
Introduction, fate maps, definitions
Cell determination = multistep process (ex: muscle)
Induction
Morphogens (ex: BMP)
Combinatorial control
Competence
Lateral inhibition
Asymmetric division/asymmetric distribution (germ cells)

Induction and competence: Eye induction in vertebrates



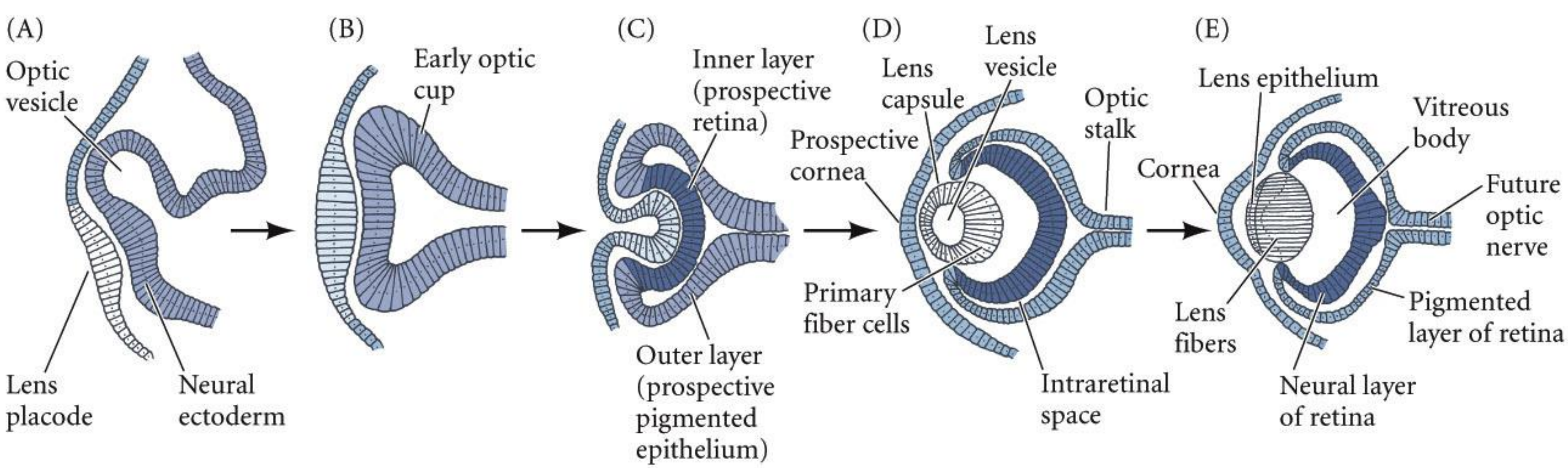
Induction and competence: Eye induction in vertebrates

Early stages of induction

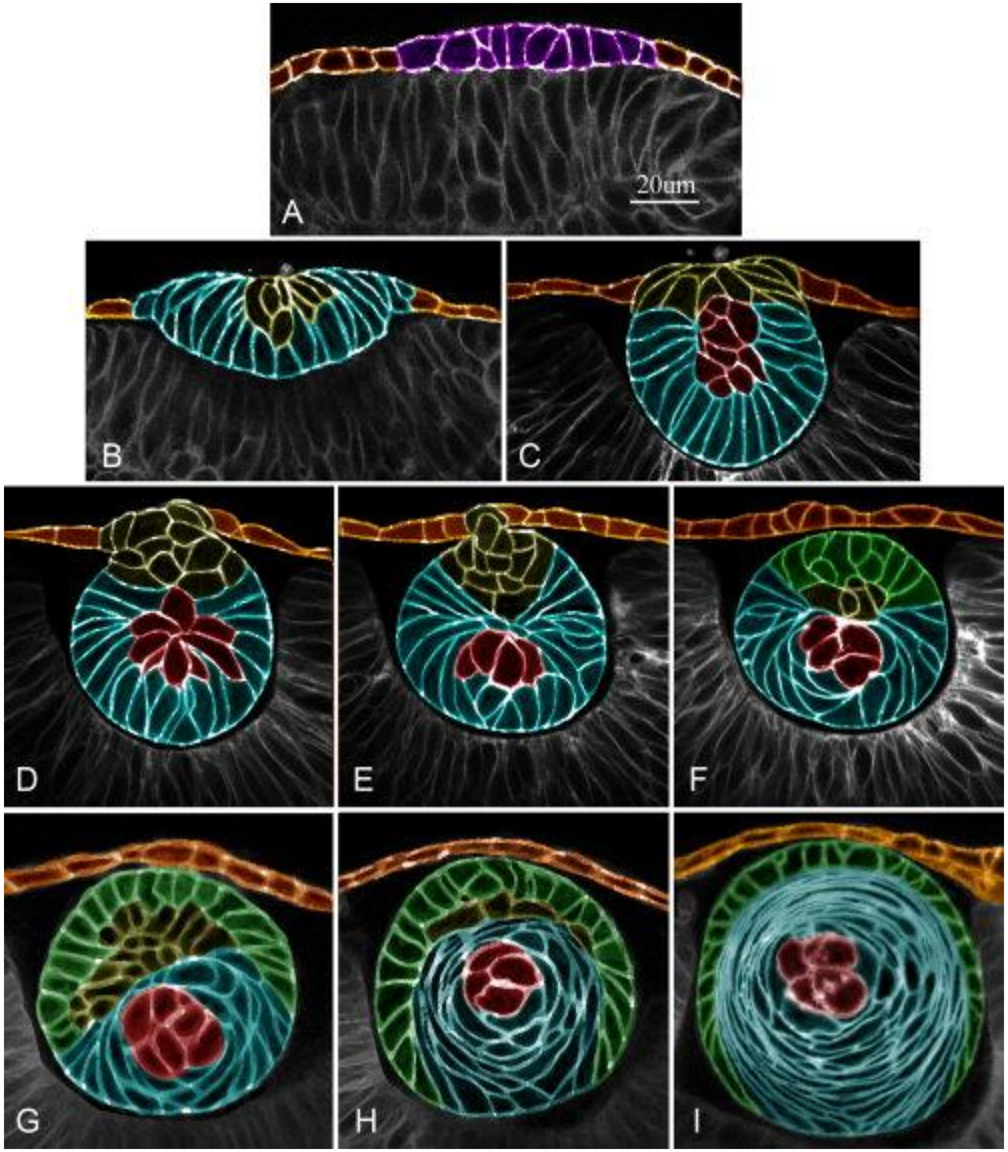


DEVELOPMENTAL BIOLOGY, 9e, Figure 3.14 (Part 2)

Formation of eye structures



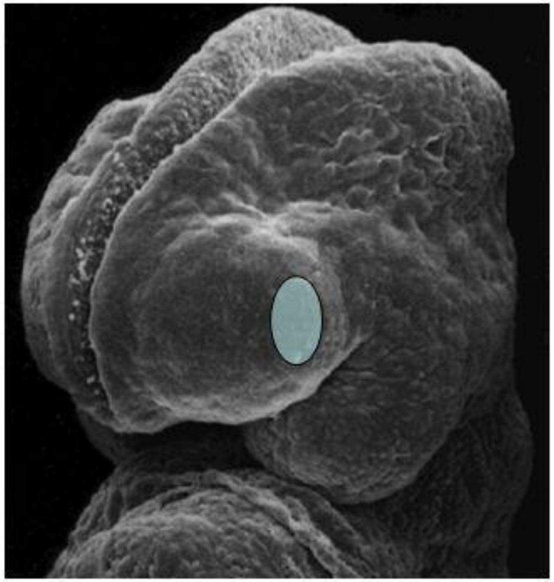
Induction and competence: Eye induction in vertebrates



Zebrafish

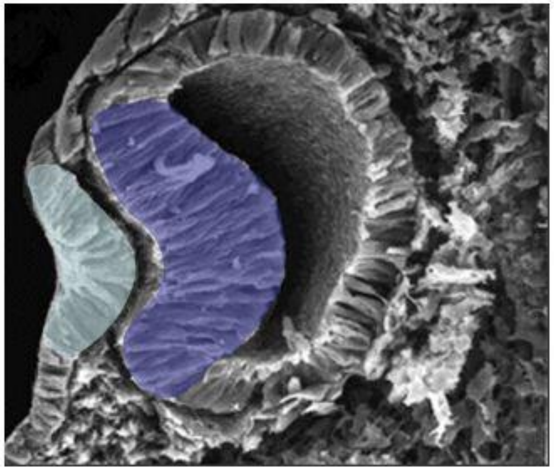
Dev Dyn. 2009 Sep;238(9):2254-65. doi: 10.1002/dvdy.21997.
Early lens development in the zebrafish: a three-dimensional time-lapse analysis.
Greiling TM1, Clark JI.

***Neuroectoderm* of optic vesicle inducing *surface ectoderm* to form lens placode**

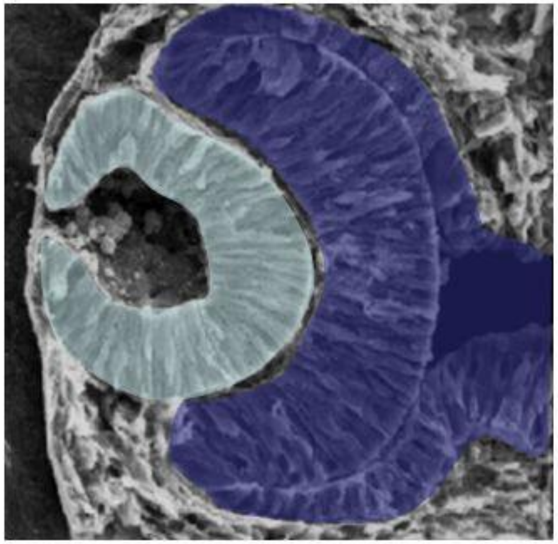


Mouse 8.5 days

The invaginating lens placode pinches off to form the lens and invagination of the optic vesicle forms the optic cup connected to the brain via the optic stalk



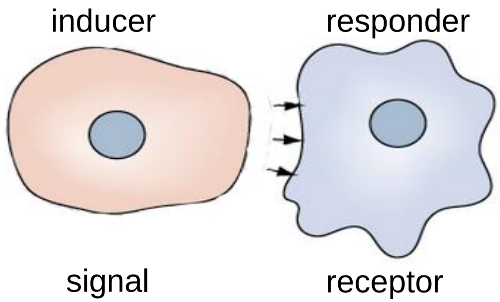
Mouse 10 days



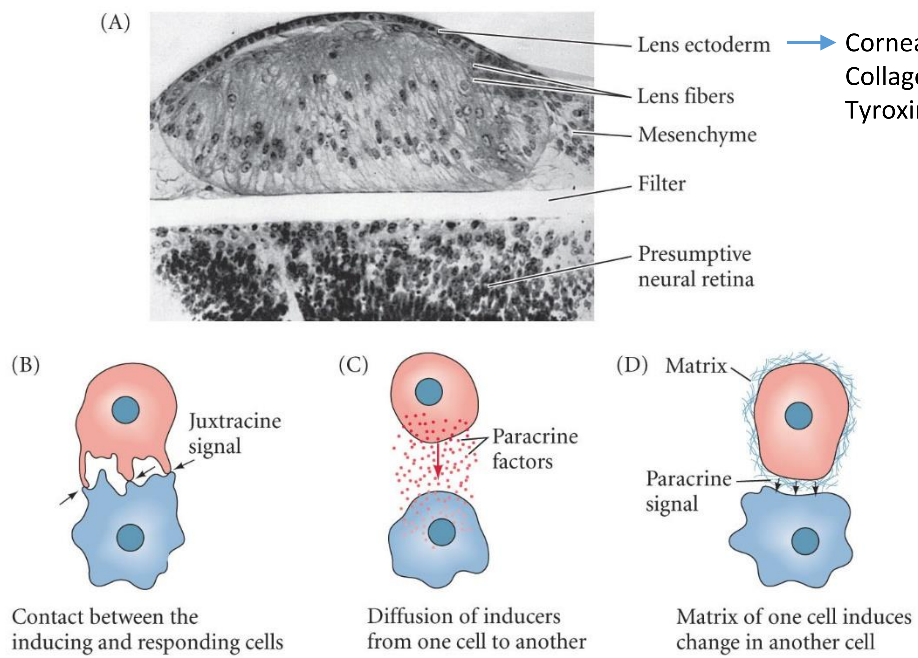
Mouse 11 days

http://www.med.unc.edu/embryo_images/

Induction and competence: Eye induction in vertebrates



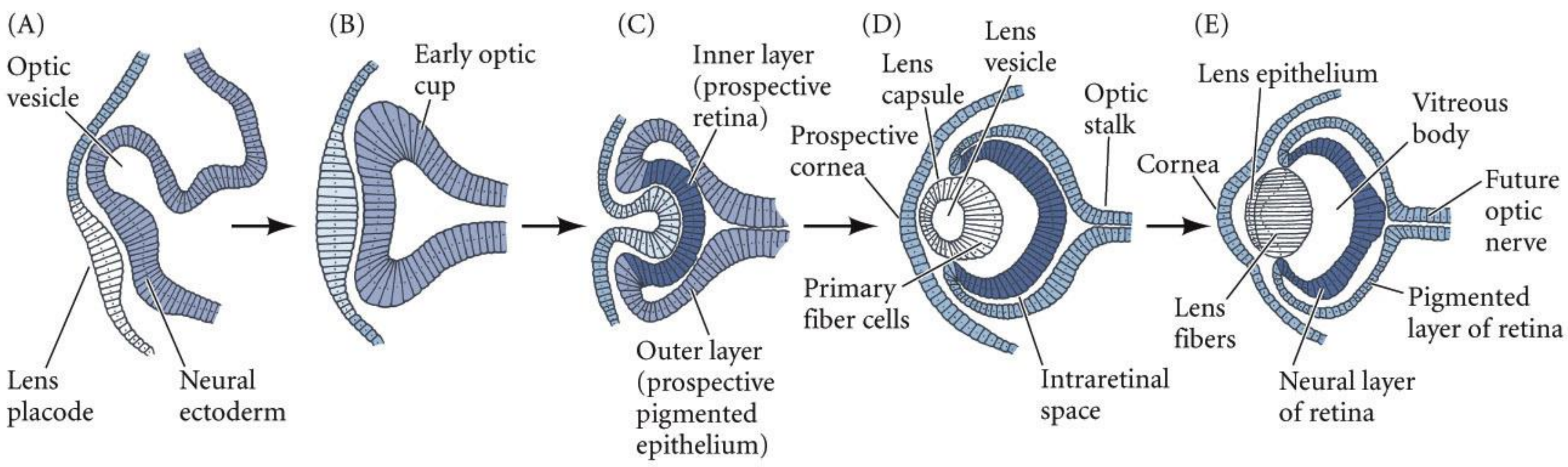
receptor
↓
signal transduction pathway
↓
changes in gene expression

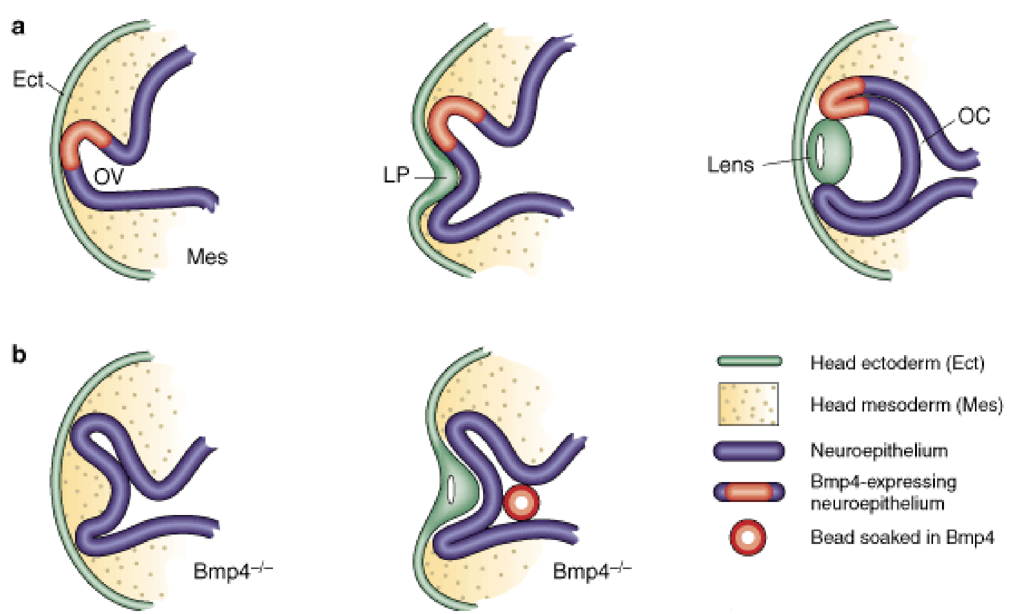


→ Cornea:
Collagen secretion
Tyroxine-> dehydration->transparent

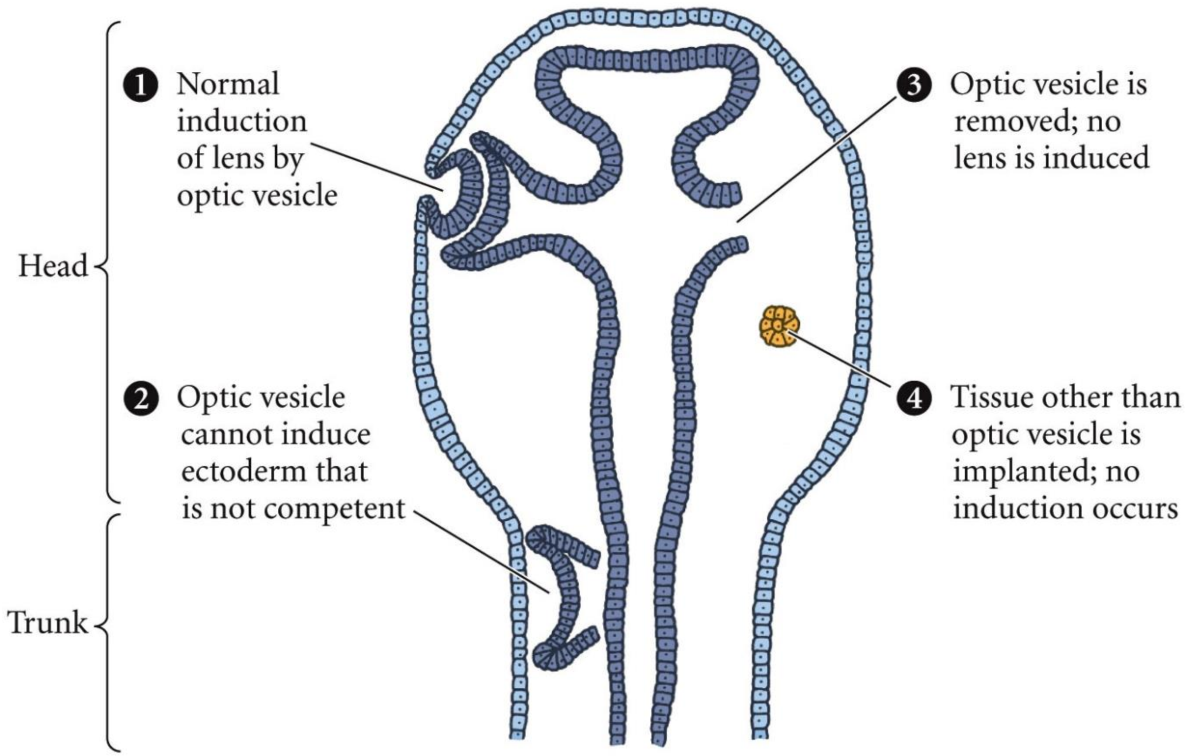
DEVELOPMENTAL BIOLOGY, Eighth Edition, Figure 6.9

Induction and competence: Eye induction in vertebrates





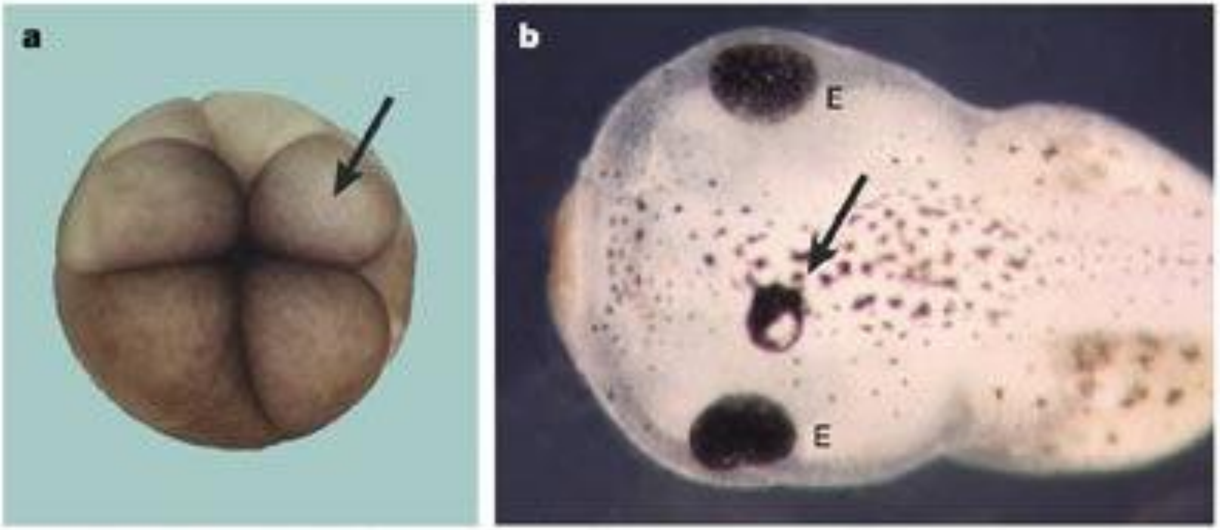
Induction and competence: Eye induction in vertebrates



DEVELOPMENTAL BIOLOGY, 9e, Figure 3.13

Induction and competence: Eye induction in vertebrates

Induction of eye in Xenopus by expression of frizzled 3

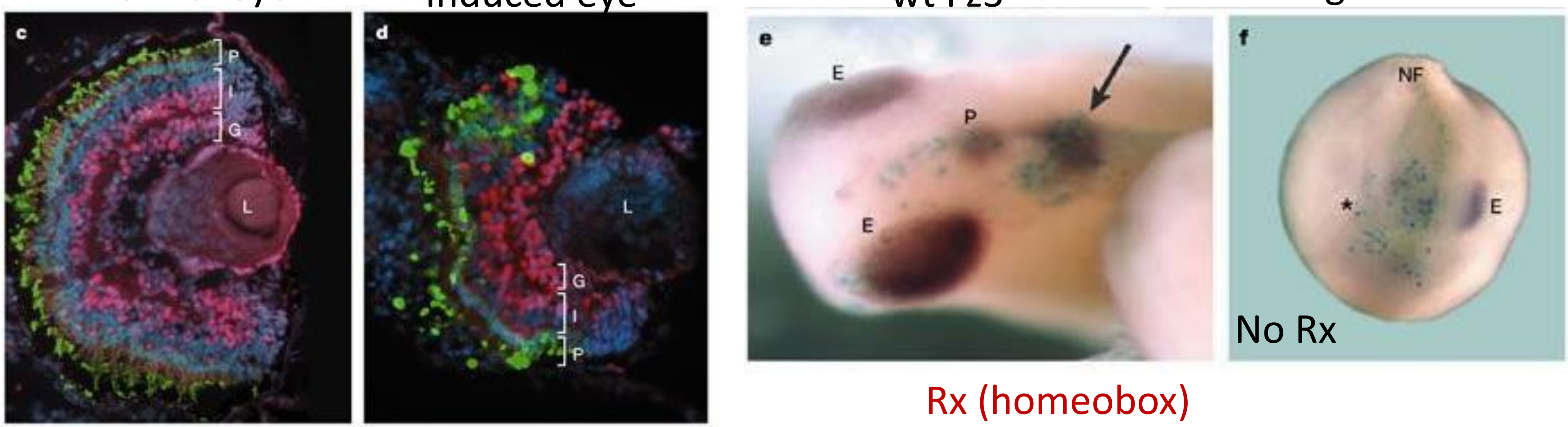


Normal eye

Induced eye

wt Fz3

Dominant negative Fz3



Pax6 Rhodopsin

Rx (homeobox)

Galactosidase (injected cells)

Induction and competence: Eye induction in vertebrates

Nat Rev Neurosci. 2001 Nov;2(11):763-71.

Cutting, pasting and painting: experimental embryology and neural development.

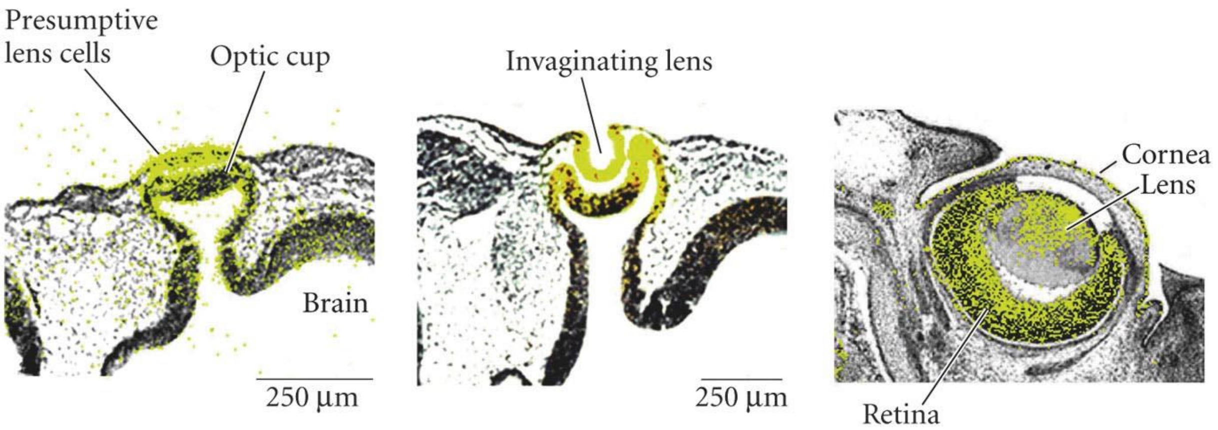
Schoenwolf GC[1].

a | A *Xenopus* embryo at the eight-cell stage. RNA is microinjected into a dorsal animal blastomere (arrow). **b** | Injection of RNA encoding the *Xenopus* receptor frizzled 3 at the eight-cell stage (molecular equivalent of pasting) causes the formation of an ectopic eye (arrow), shown here in an embryo at developmental stage 45 (E, eye). **c** | Immunolabelling of a section through a normal eye from an embryo at stage 42. Anti-Pax6 (paired box 6) antibodies (red) label ganglion cells in the ganglion cell layer (G) and amacrine cells in the inner nuclear layer (I), whereas anti-rhodopsin antibodies (green) label rod photoreceptors in the photoreceptor layer (P). L indicates the lens, which is nonspecifically labelled. **d** | Immunolabelling of a section through an ectopic eye using the same antibodies as in **c**. The retina of the ectopic eye has a similar laminar organization to that found in the normal eye. **e** | Injection of RNA encoding *Xenopus* frizzled 3 at the eight-cell stage (molecular equivalent of pasting) causes the ectopic expression of the retinal homeobox gene *Rx* (arrow), shown here by *in situ* hybridization of an embryo at stage 28 (dorsal view; E, labelling of the endogenous eyes; P, labelling of the pineal gland). Co-injection of RNA encoding β-galactosidase allows the identification of tissue derived from the injected blastomere (sky blue; molecular equivalent of painting). **f** | Injection of RNA encoding a dominant-negative form of frizzled 3, consisting of the soluble extracellular ligand-binding region (molecular equivalent of cutting), prevents the expression of *Rx* on the injected side (asterisk) in a stage-18 embryo (rostral view). This effect correlates with suppression of eye development on the injected side (NF, fusing neural folds). The injected side is marked by co-expression of β-galactosidase. Photograph in part **a** courtesy of T. Van Raay in the M. Vetter laboratory; parts **b**–**f** reproduced with permission from Ref. 67 © 2001 National Academy of Sciences, USA.

Rasmussen, J. T., Deardorff, M. A., Tan, C., Rao, M. S., Klein, P. S. & Vetter, M. L. *Regulation of eye development by frizzled signaling in Xenopus*. *Proc. Natl Acad. Sci. USA* **98**, 3861–3866 (2001).

Induction and competence: Eye induction in vertebrates

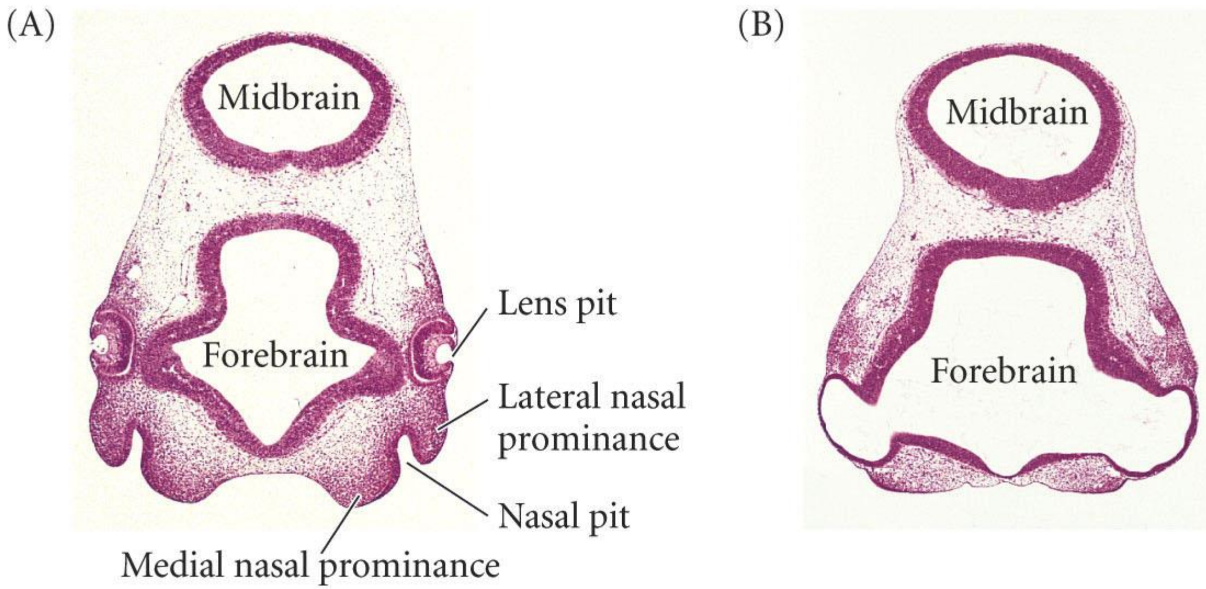
Pax6 expression



DEVELOPMENTAL BIOLOGY, Seventh Edition, Figure 4.17 Sinauer Associates, Inc.

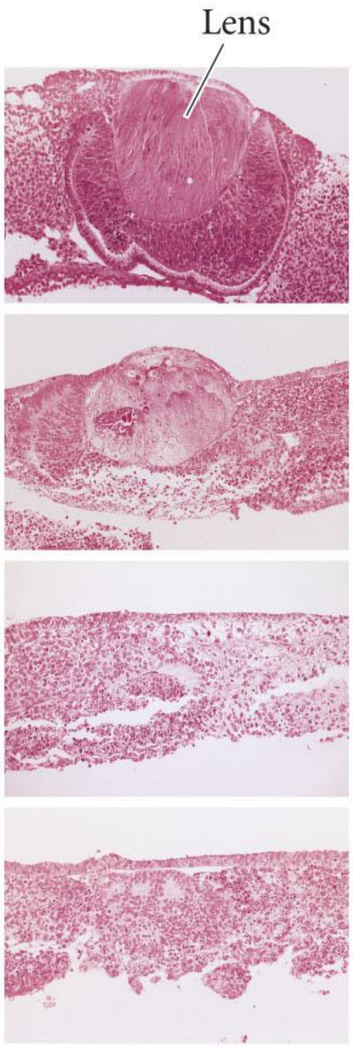
Induction and competence: Eye induction in vertebrates

Pax6 -/-



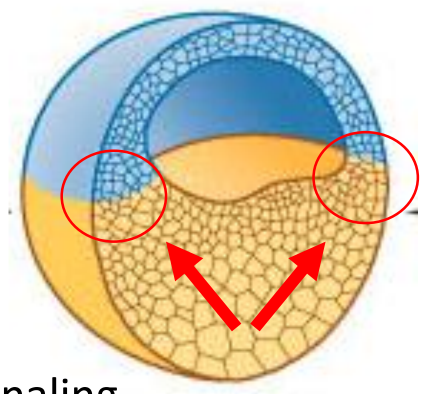
Induction and competence: Eye induction in vertebrates

Optic vesicles	Surface ectoderm	Lens induction
Wild-type	Wild-type	Yes
Pax6$^-$/*Pax6*$^-$	Wild-type	Yes
Wild-type	*Pax6*$^-$/*Pax6*$^-$	No
Pax6$^-$/*Pax6*$^-$	*Pax6*$^-$/*Pax6*$^-$	No

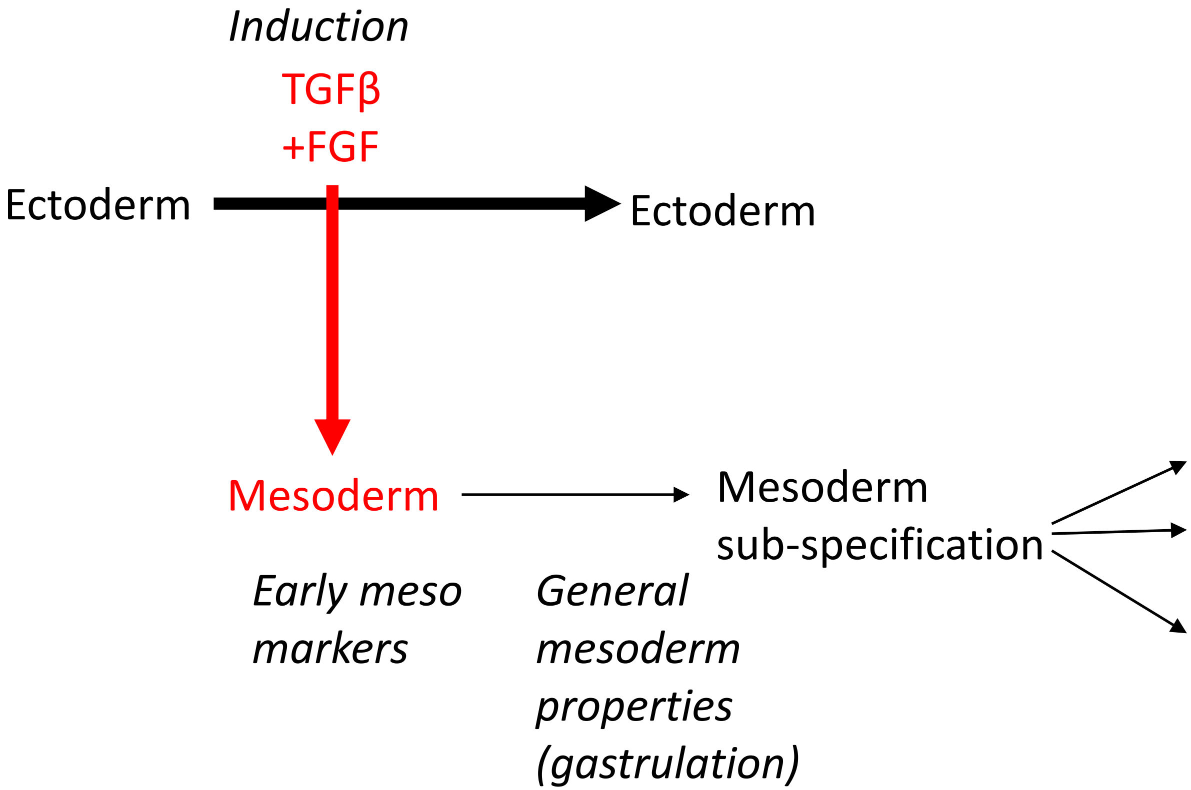


DEVELOPMENTAL BIOLOGY, Eighth Edition, **Figure 6.3**

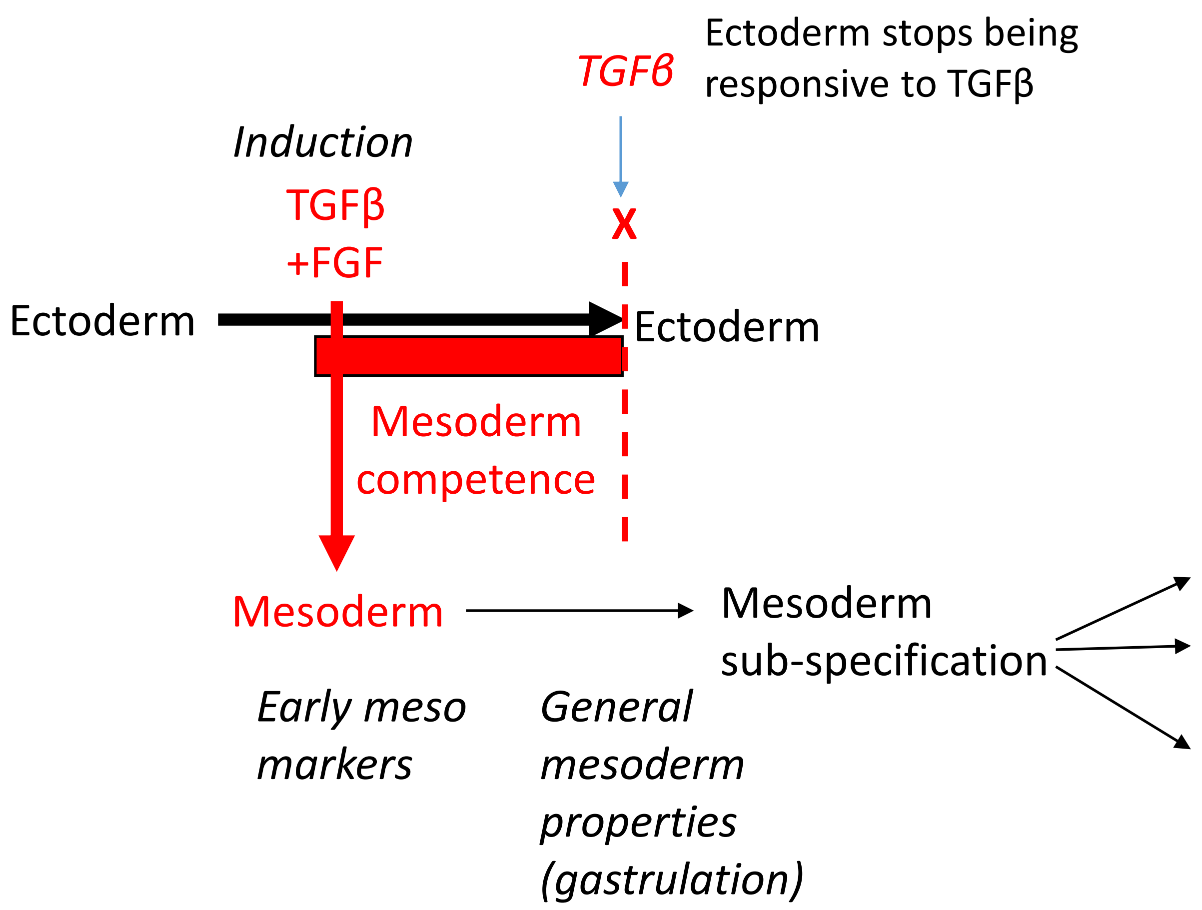
Competence
Example of mesoderm competence in vertebrates (Xenopus)



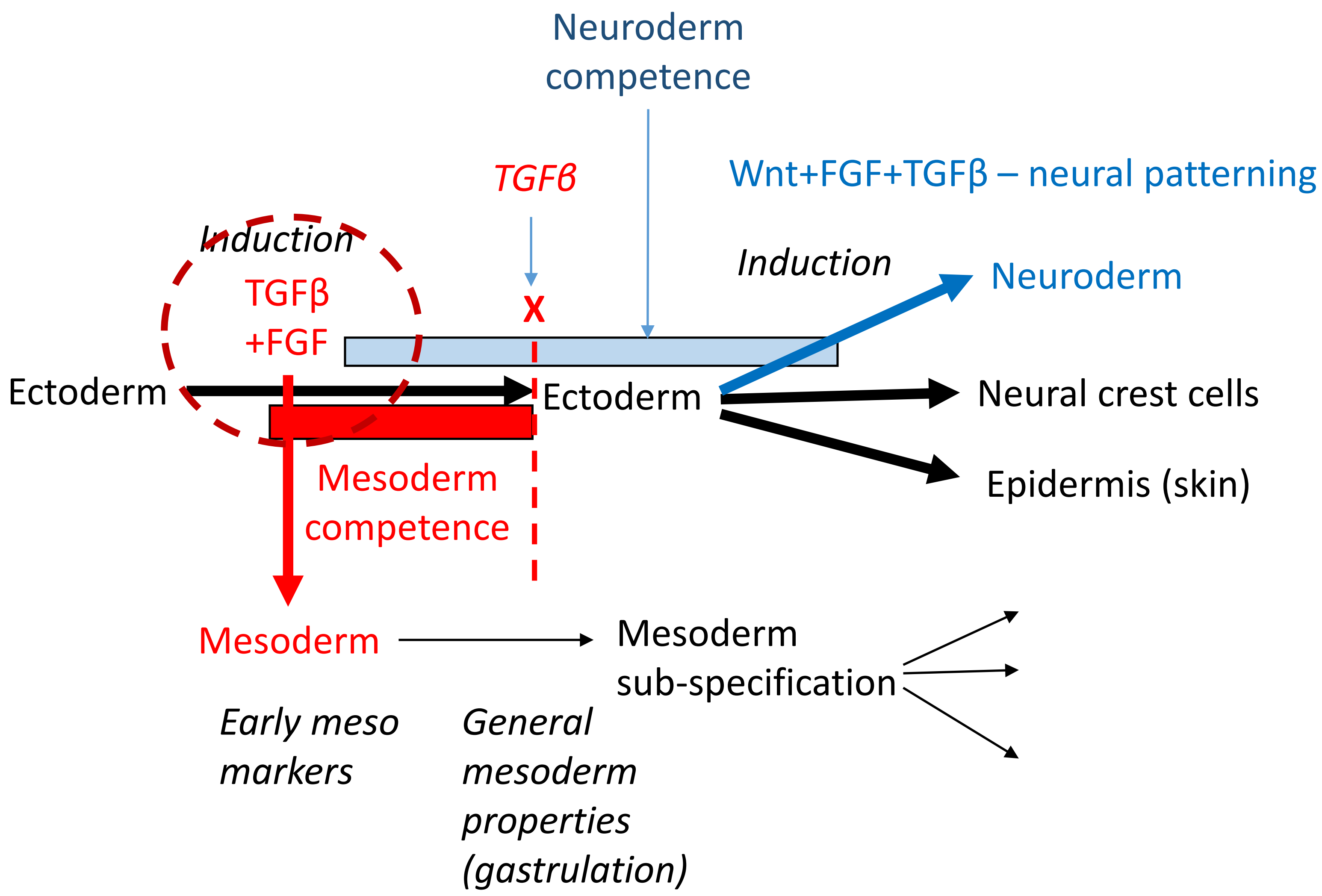
Competence
Example of mesoderm competence in vertebrates (Xenopus)



Competence
Example of mesoderm competence in vertebrates (Xenopus)



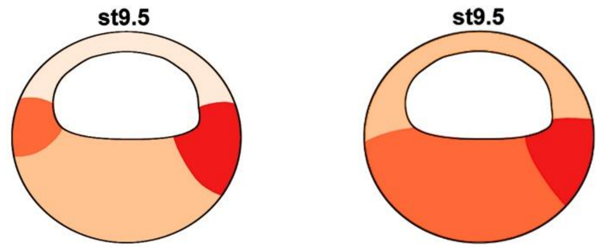
Competence
Example of mesoderm competence in vertebrates (Xenopus)



Competence
Example of mesoderm competence in vertebrates (Xenopus)

FGF

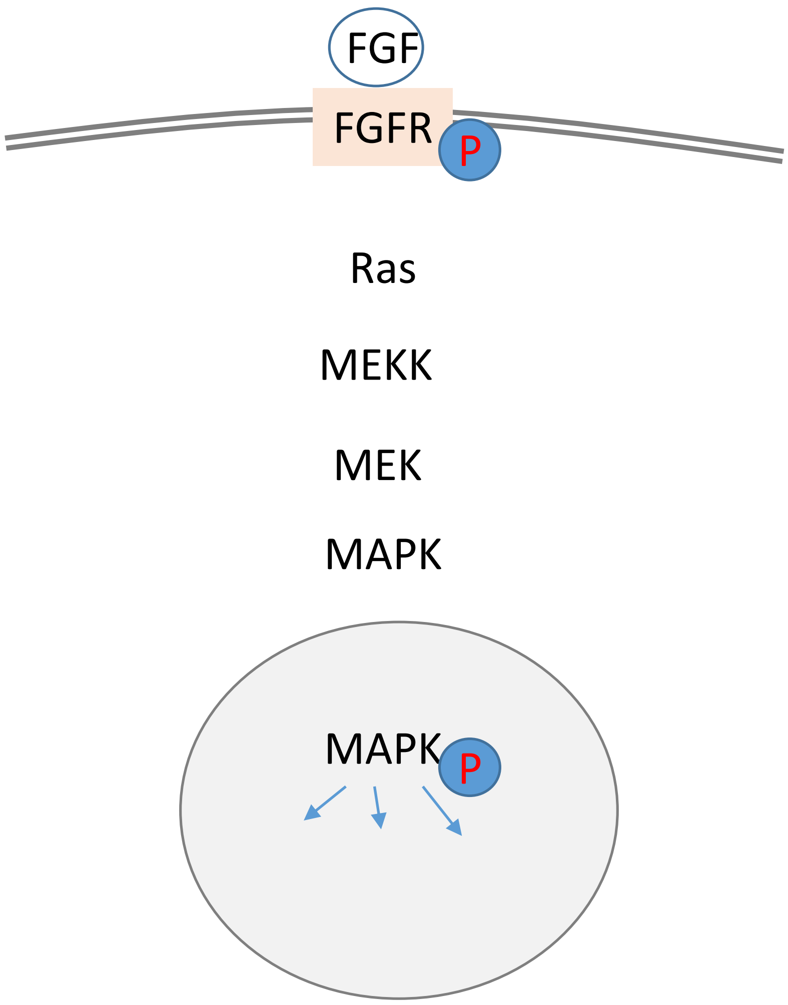
TFGβ
(Nodals)



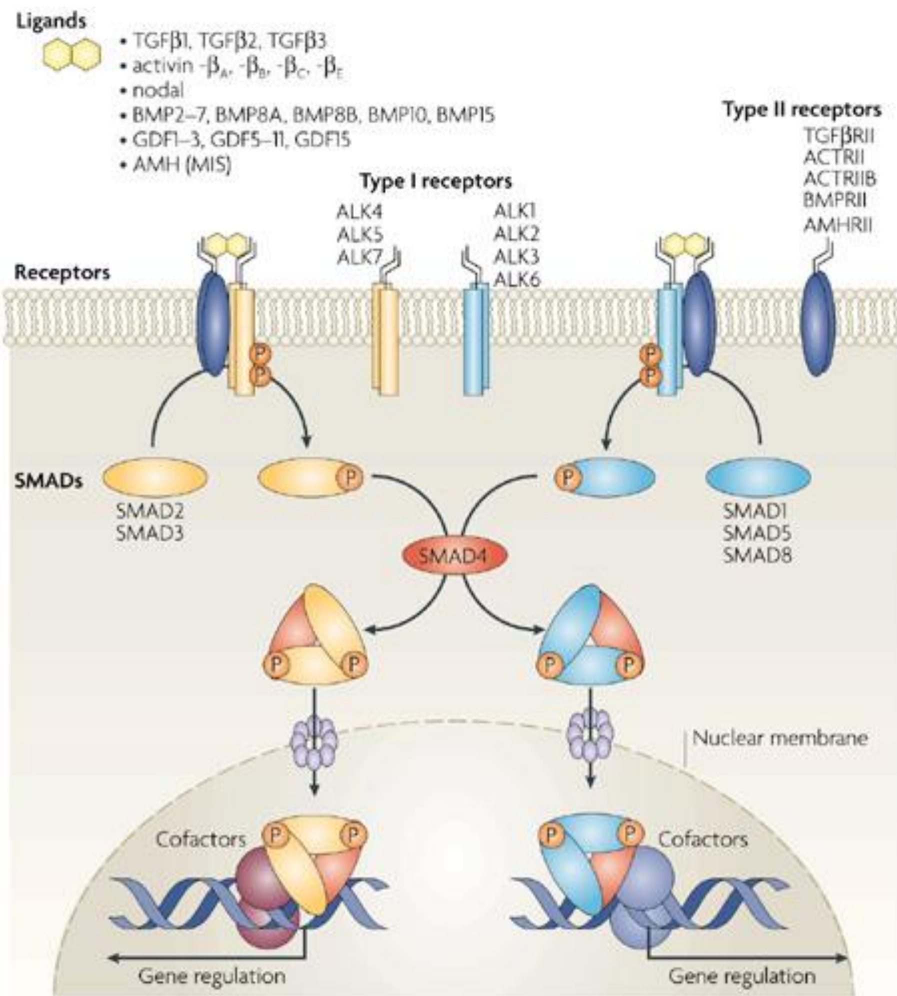
MAPK

Smad2

FGF signaling



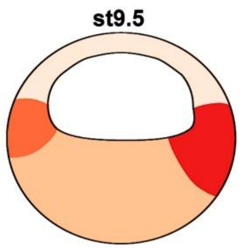
TGFβ signaling



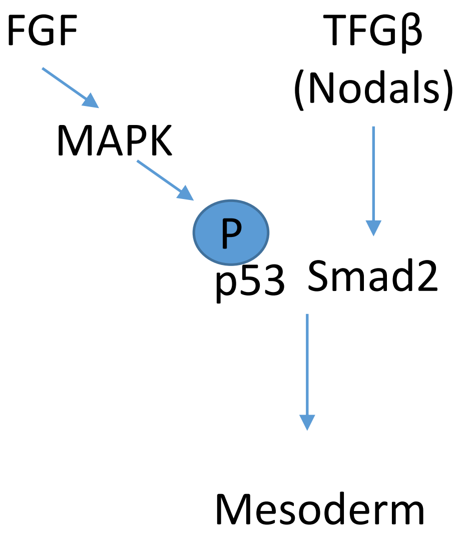
Nature Reviews | Molecular Cell Biology

TGFβ + FGF signaling and mesoderm induction

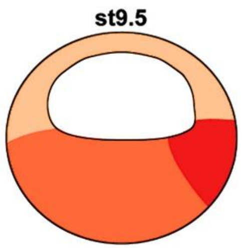
FGF



MAPK

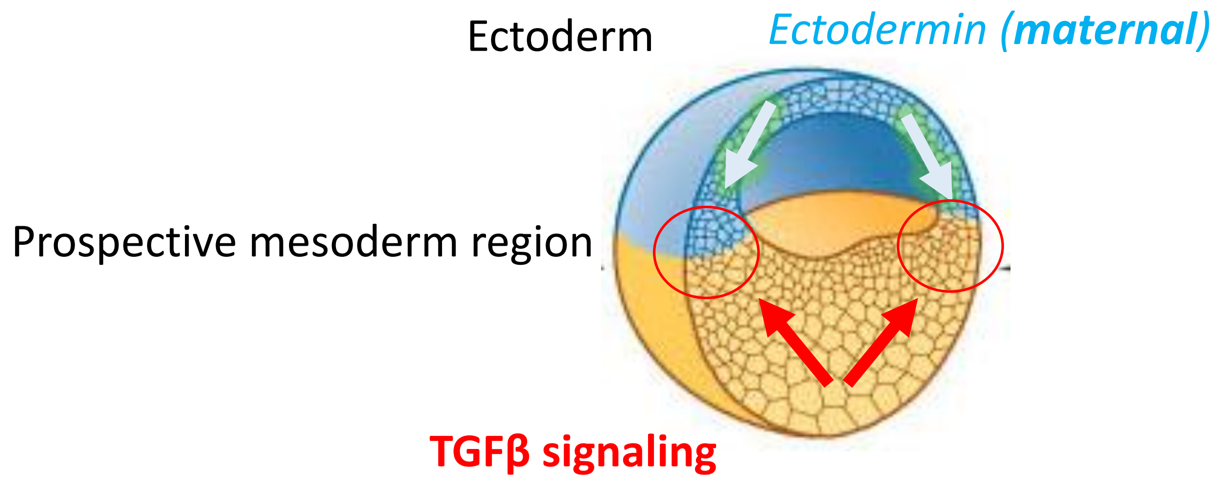


TFGβ
(Nodals)



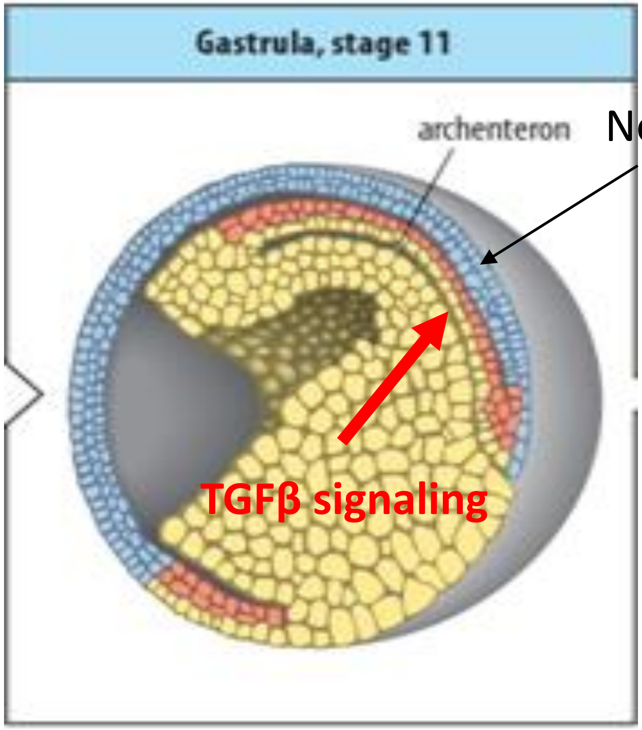
Smad2

Competence
Example of mesoderm competence in vertebrates (Xenopus)



Ectodermin = Ubiquitin ligase -> targets Smad4 for degradation
-> restricts mesoderm induction

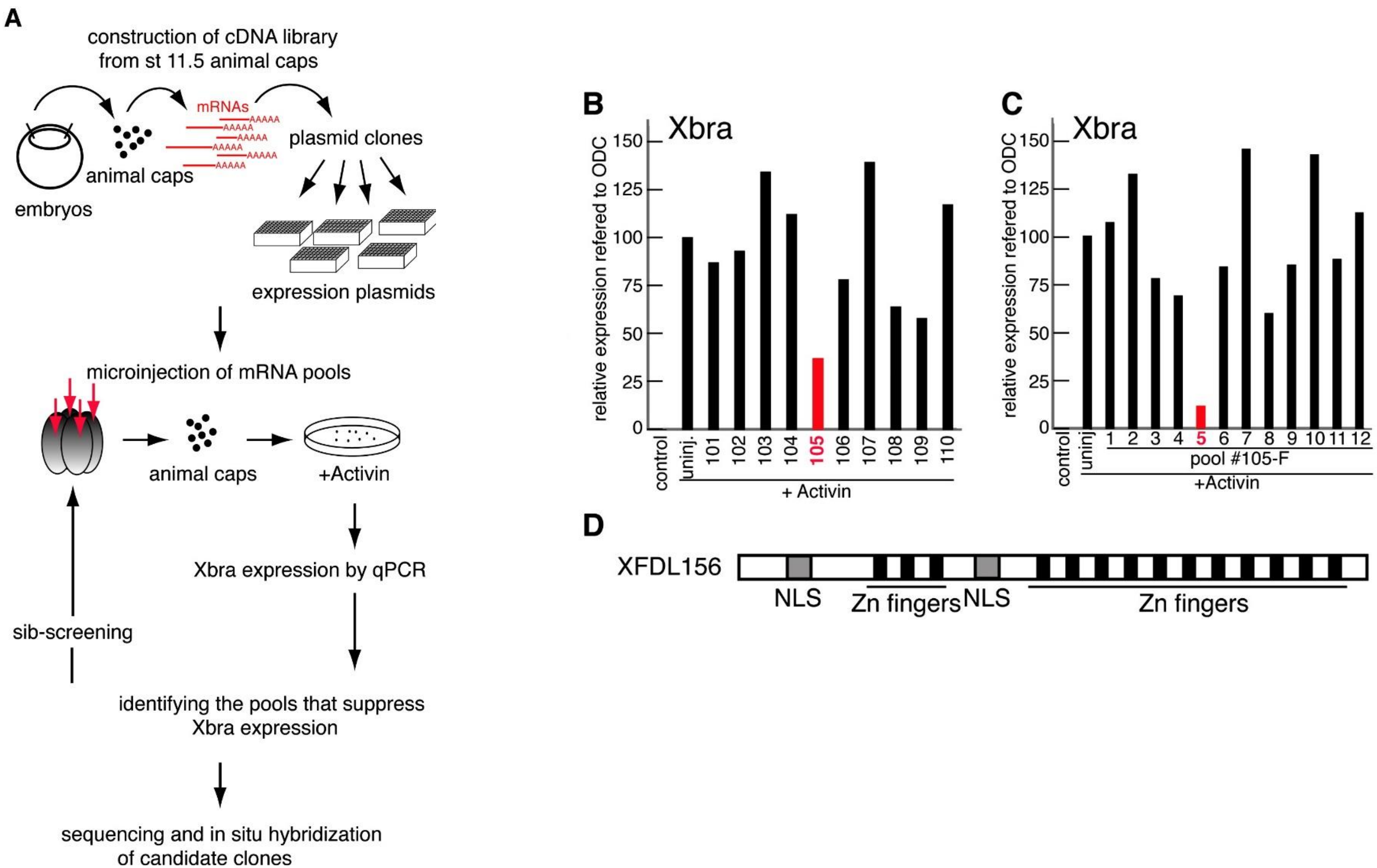
Competence
Example of mesoderm competence in vertebrates (Xenopus)



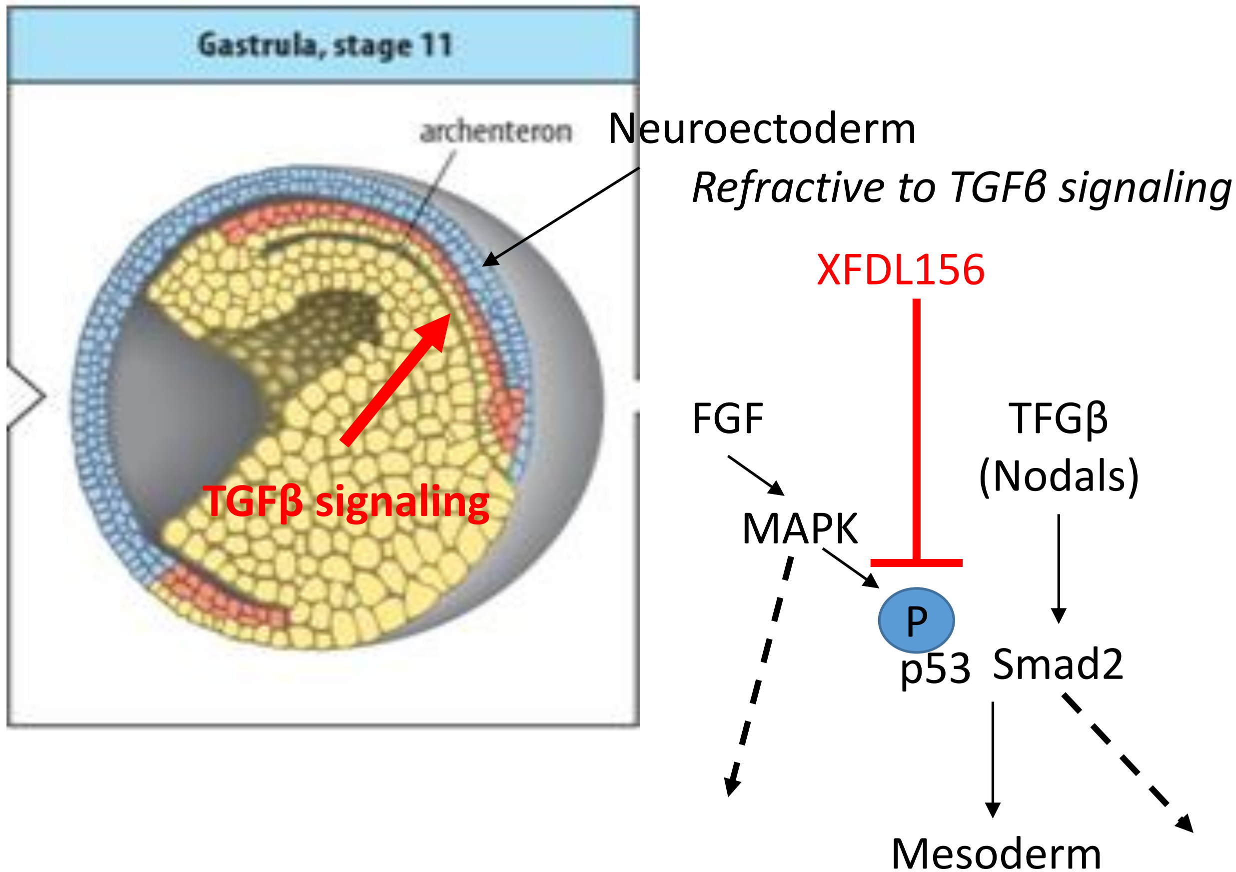
Ectodermal Factor Restricts Mesoderm Differentiation by Inhibiting p53

Cell 133, 878–890, May 30, 2008

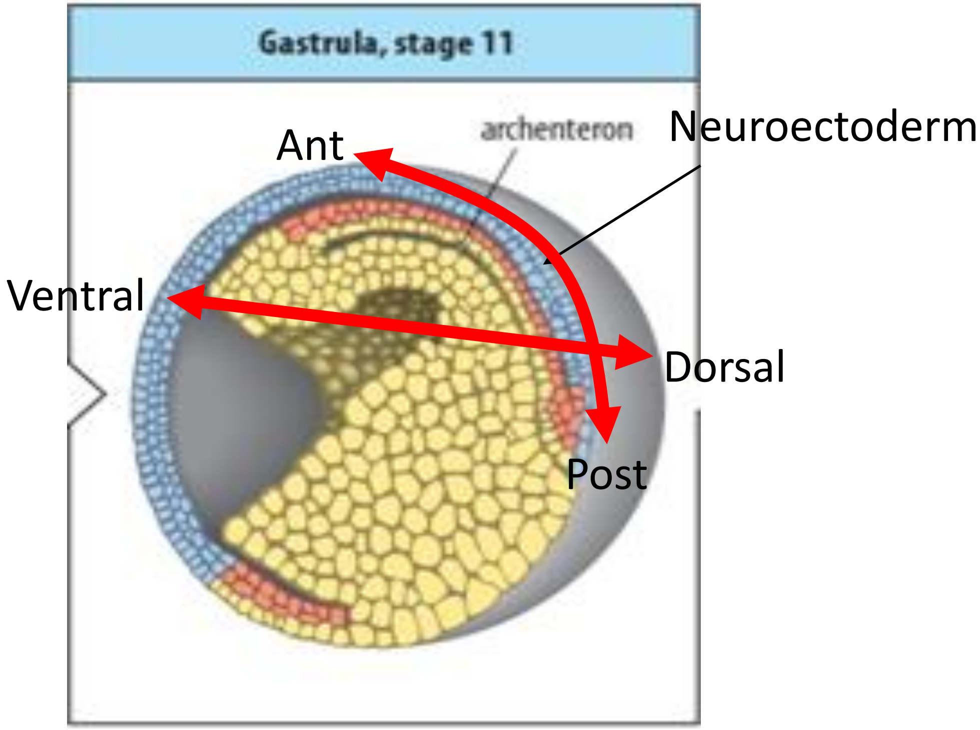
Noriaki Sasai,[1,*] Rieko Yakura,[1] Daisuke Kamiya,[1] Yoko Nakazawa,[1] and Yoshiki Sasai[1,*]
[1]Organogenesis and Neurogenesis Group, RIKEN Center for Developmental Biology, Kobe 650-0047, Japan
*Correspondence: norisa@cdb.riken.jp (N.S.), yoshikisasai@cdb.riken.jp (Y.S.)
DOI 10.1016/j.cell.2008.03.035



Competence
Example of mesoderm competence in vertebrates (Xenopus)



Competence
Example of mesoderm competence in vertebrates (Xenopus)



FGF-MAPK and TFGβ-Smad signaling can now be used for other functions
-> dorso-ventral and anterior-posterior patterning

Cell fate commitment/specification/determination

Plasticity!

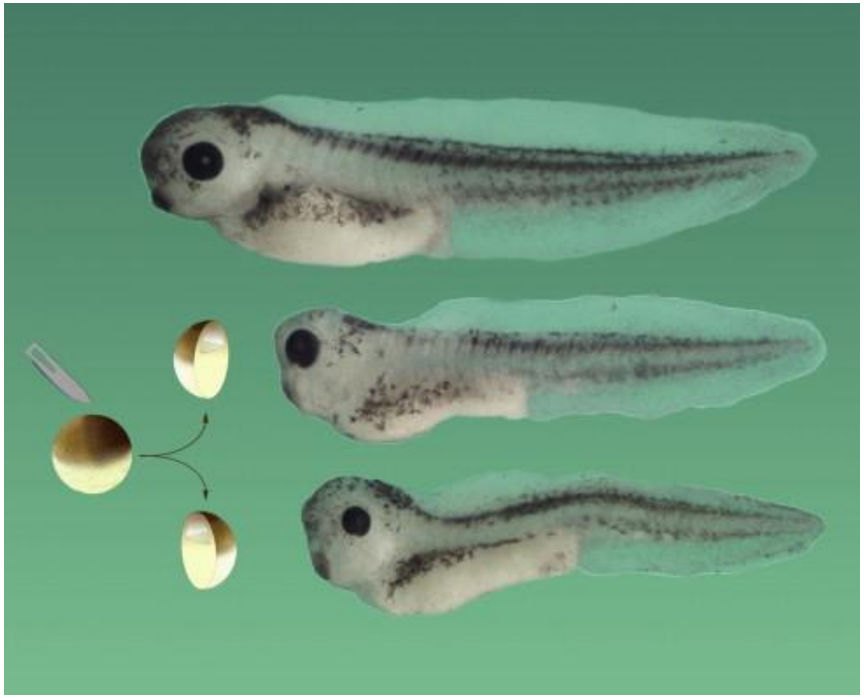
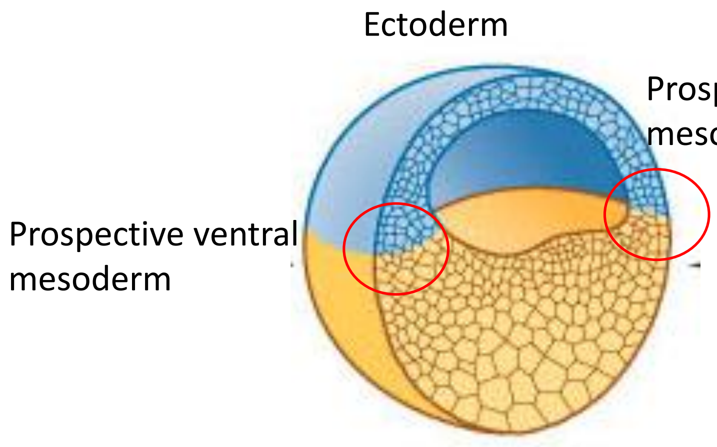
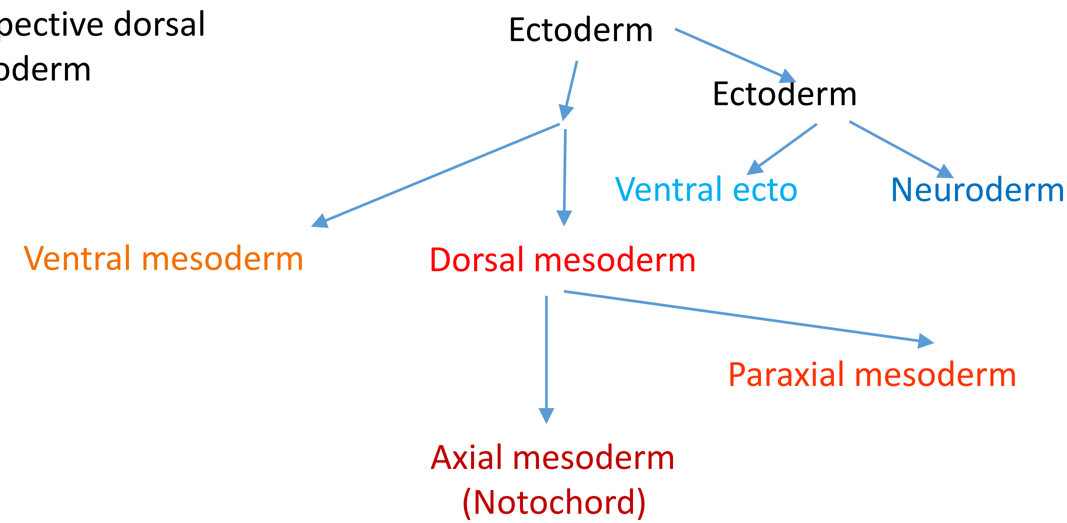


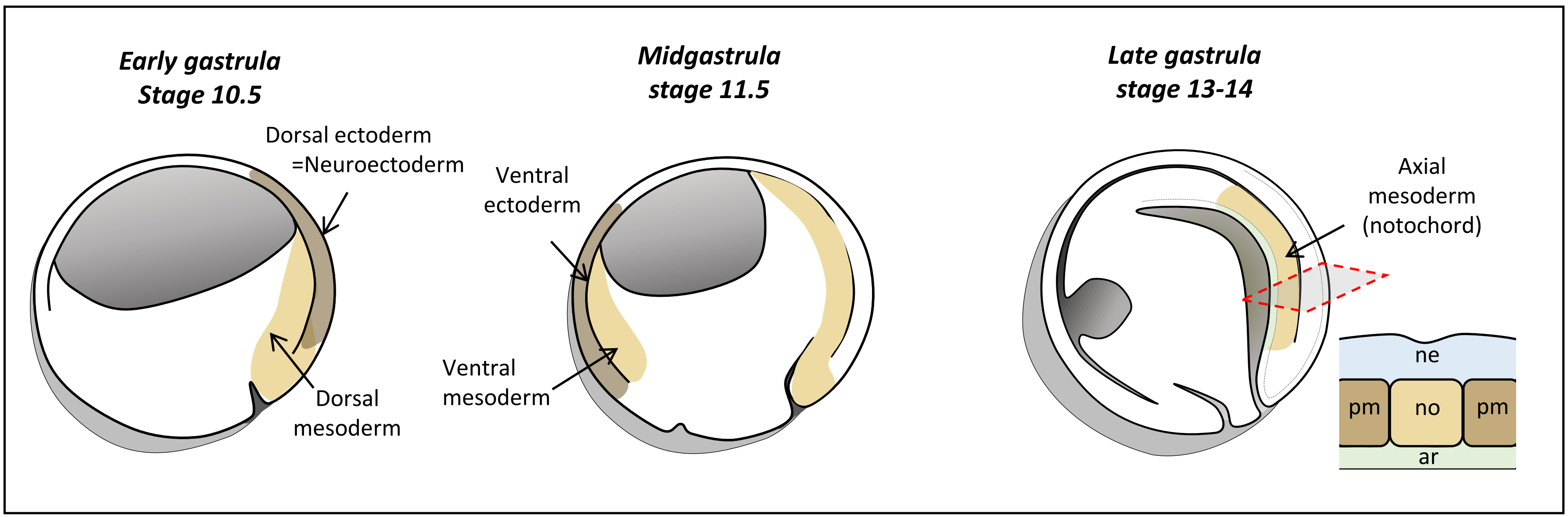
Fig. 2. In *Xenopus*, the blastula constitutes a self-differentiating morphogenetic field, in which cells are able to communicate over long distances. When the blastula is bisected with a scalpel blade, identical twins can be obtained, provided that both fragments retain Spemann's organizer tissue. Thus a half-embryo can regenerate the missing half. In humans, identical twins are found in three out of 1000 live births, and usually arise from the spontaneous separation of the inner cell mass of the blastocyst into two. A normal tadpole is shown on top, and two identical twins derived from the same blastula below, all at the same magnification. Reproduced from De Robertis, 2006, with permission of Nature Reviews.

Cell fate commitment/specification/determination

Plasticity!

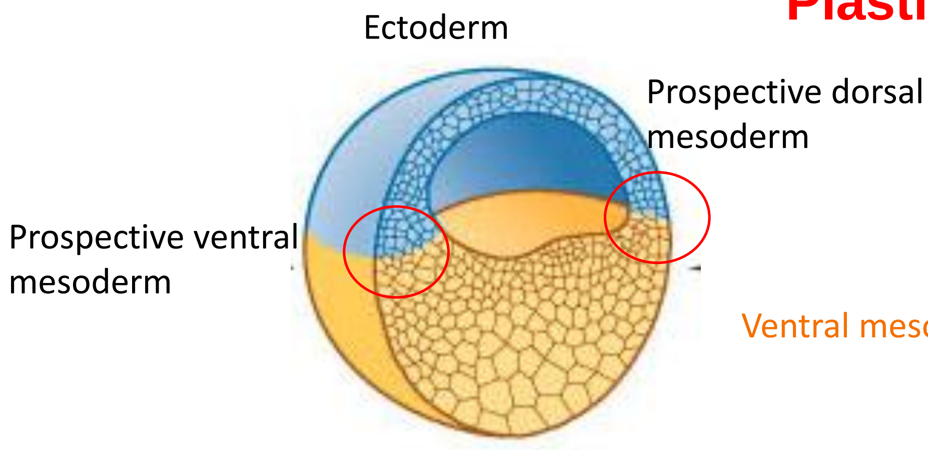


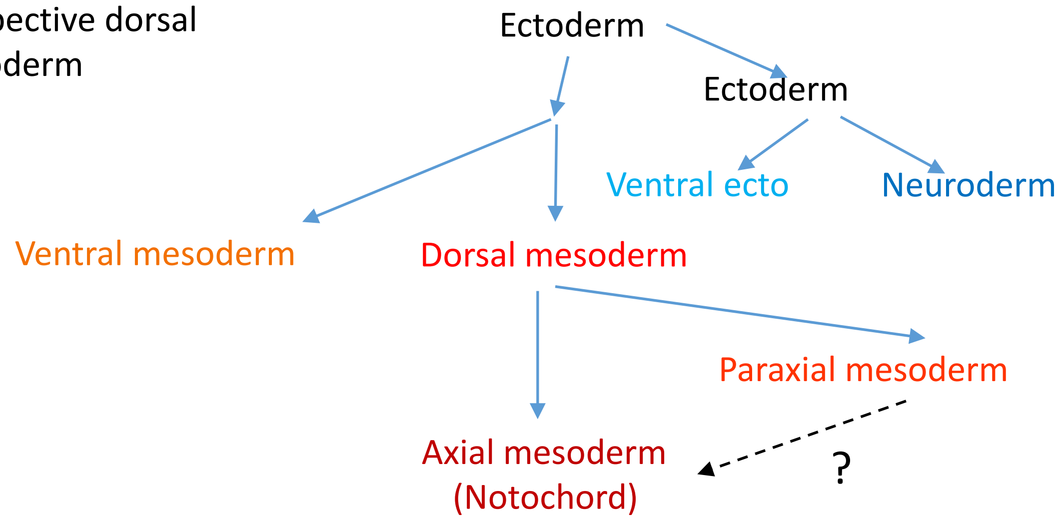




Cell fate commitment/specification/determination

Plasticity!





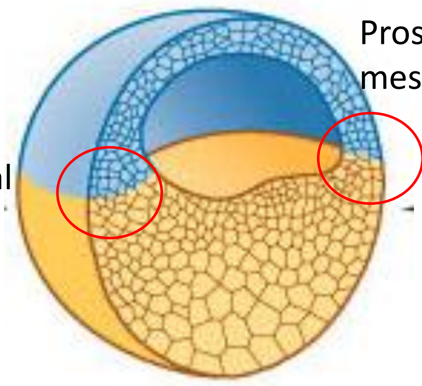
Cell fate commitment/specification/determination

Plasticity!

Ectoderm

Prospective dorsal mesoderm

Prospective ventral mesoderm



Ectoderm

Ectoderm

Ventral ecto

Neuroderm

Ventral mesoderm

Dorsal mesoderm

Paraxial mesoderm

Axial mesoderm (Notochord)

?

Determination

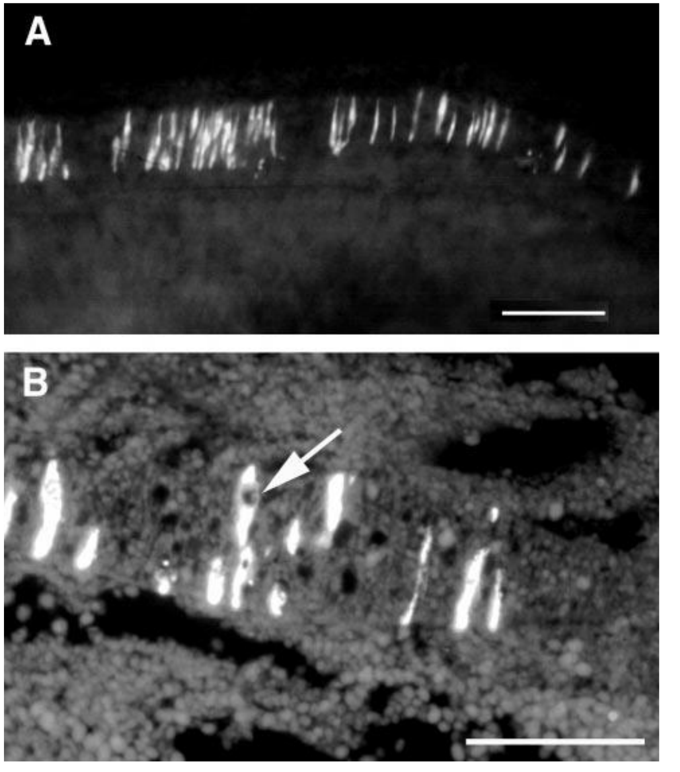
Cell fate commitment/specification/determination

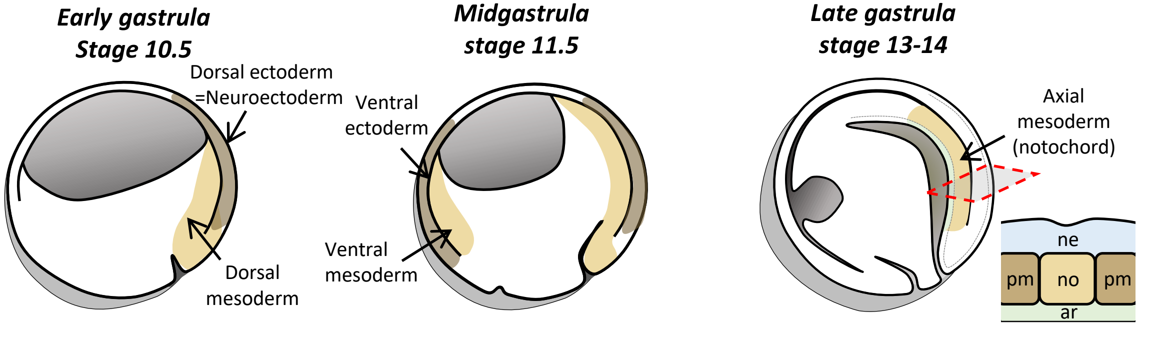
Plasticity!

Developmental Biology 225, 226–240 (2000)
doi:10.1006/dbio.2000.9769, available online at http://www.idealibrary.com on IDEAL®

Cells Remain Competent to Respond to Mesoderm-Inducing Signals Present during Gastrulation in *Xenopus laevis*

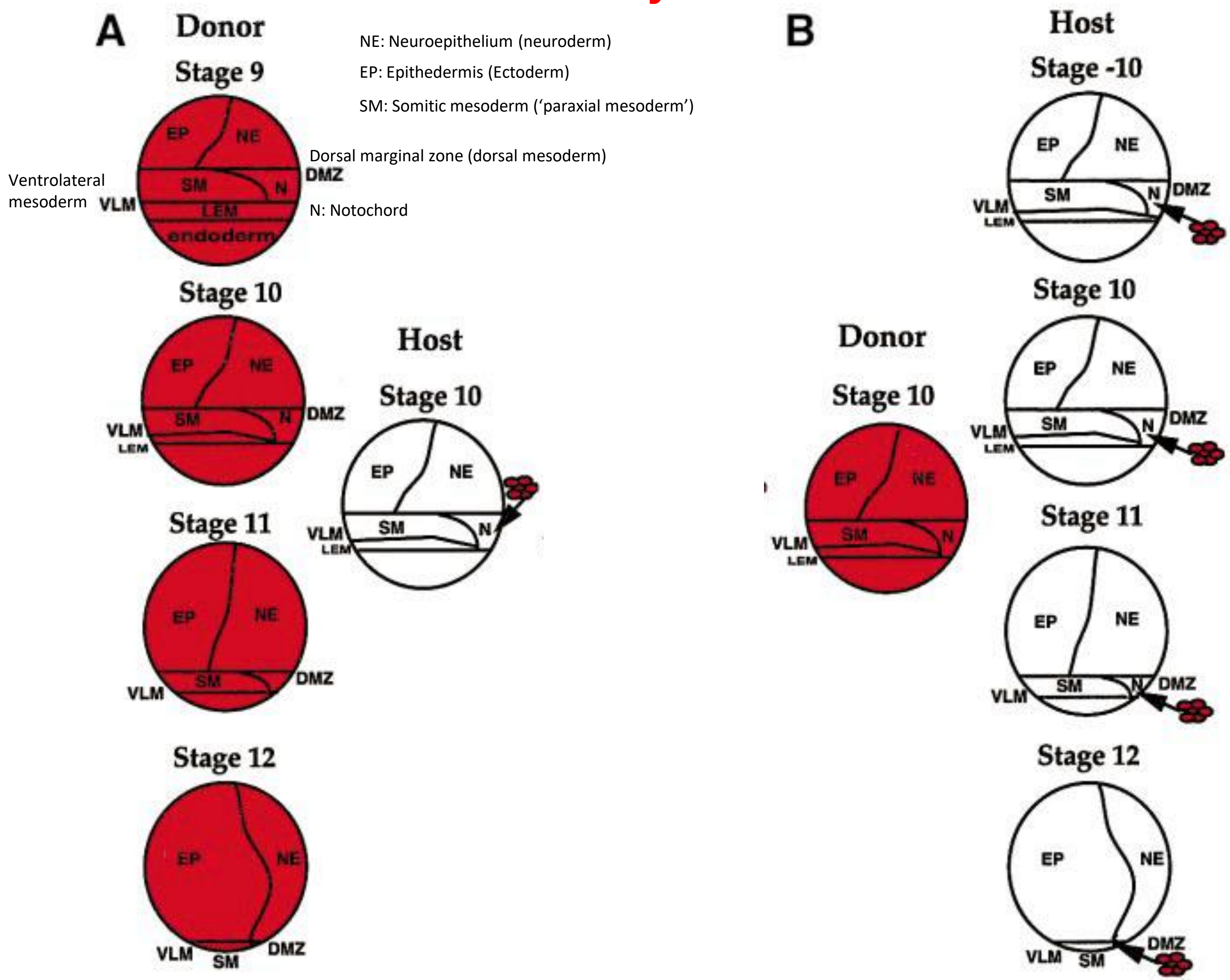
Carmen Domingo*[,1] and Ray Keller†
*Department of Biology, San Francisco State University, San Francisco, California 94132; and †Department of Biology, University of Virginia, Charlottesville, Virginia 22903





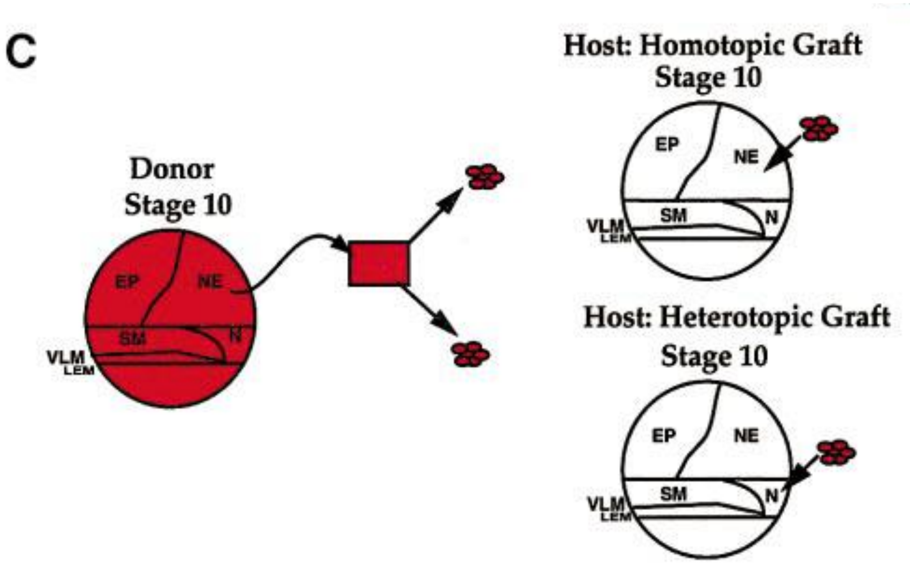
Cell fate commitment/specification/determination

Plasticity!



Cell fate commitment/specification/determination

Plasticity!



Cell fate commitment/specification/determination

Plasticity!

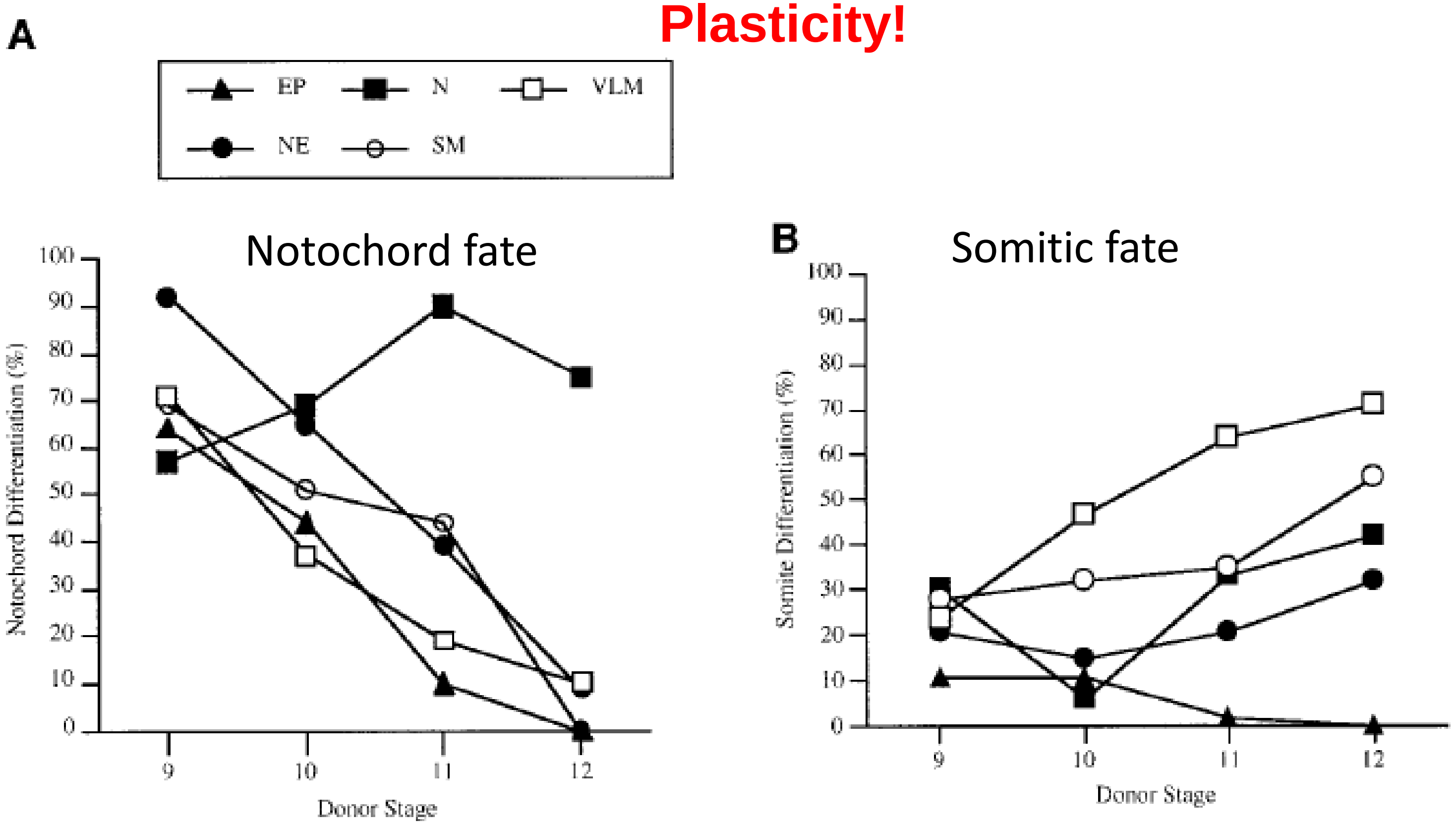


FIG. 8. Stage-dependent competence to form notochord and somites. (A) A line graph shows the percentage of cases in which grafted cells gave rise to notochord cells. The y axis represents the percentage of cases in which grafted cells differentiated into notochord cells. The x axis represents the age of the donor embryos. (B) A line graph shows the percentage of cases in which grafted cells gave rise to somitic cells. The y axis represents the percentage of cases in which grafted cells differentiated into somitic cells. The x axis represents the age of the donor embryos. EP, epidermis; NE, neural ectoderm; N, notochord; SM, somitic mesoderm; VLM, ventrolateral mesoderm.

Cell fate commitment/specification/determination

Plasticity!

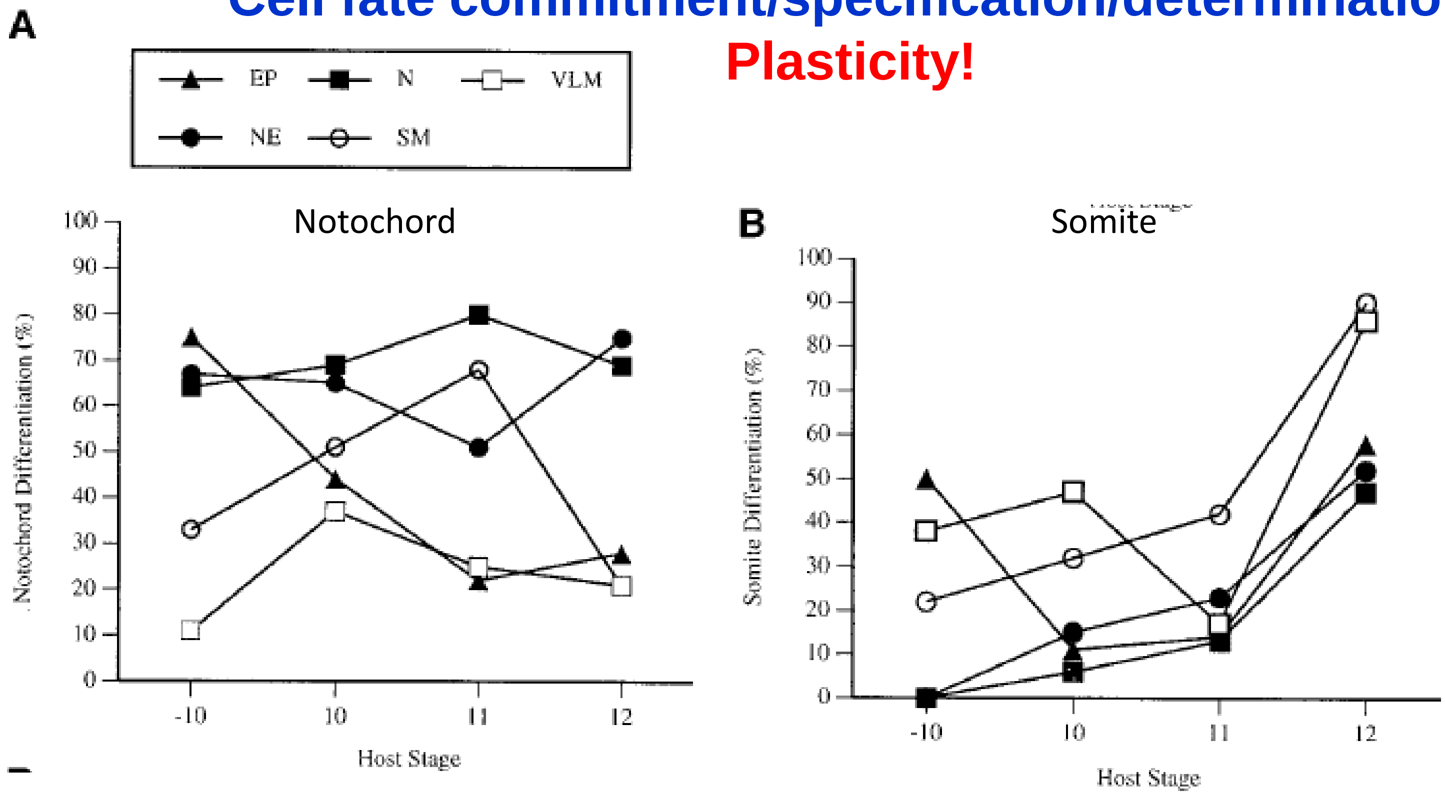
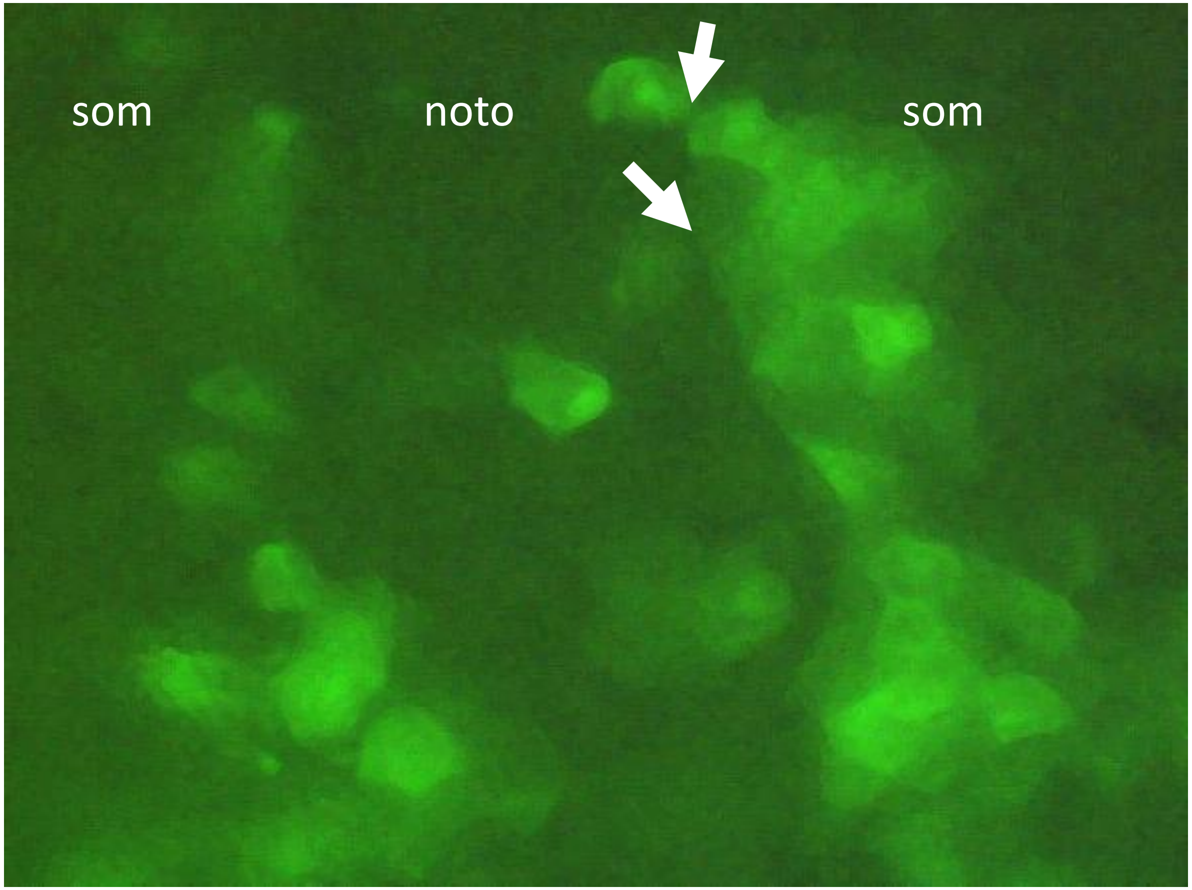


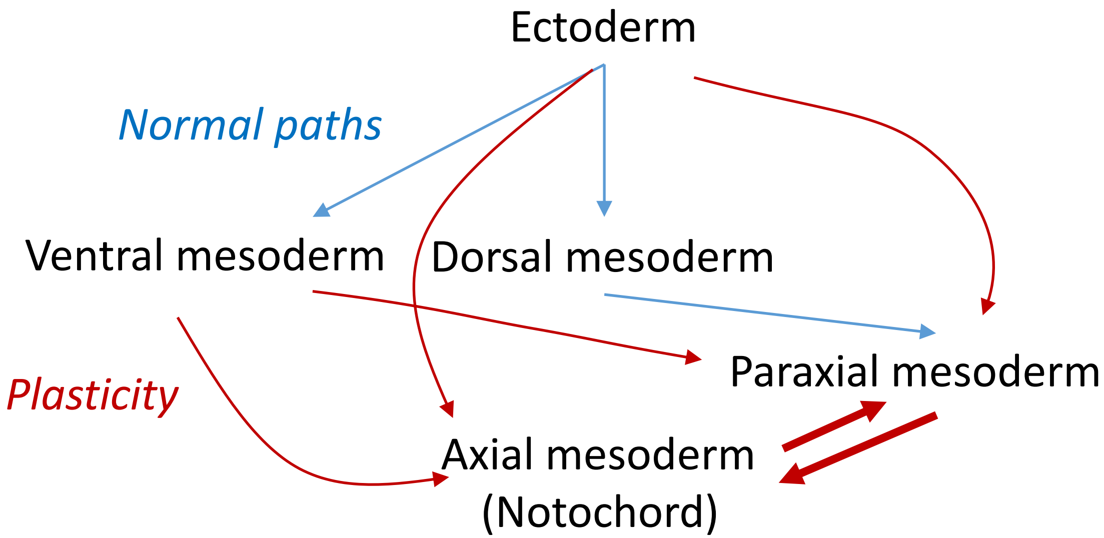
FIG. 9. Notochord-inducing signals persist through gastrula stages and overlap with somite-inducing signals throughout gastrulation. (A) A line graph shows the percentage of cases in which grafted cells gave rise to notochord cells. The *y* axis represents the percentage of cases in which grafted cells differentiated into notochord cells. The *x* axis represents the age of the host embryos. (B) A line graph shows the percentage of cases in which grafted cells gave rise to somitic cells. The *y* axis represents the age of the host embryos. EP, epidermis; NE, neural ectoderm; N, notochord; SM, somitic mesoderm; VLM, ventrolateral mesoderm.

Forced commitment to somitic fate
(overexpression of β-catenin) – activated Wnt signaling



Reintsch WE, Habring-Mueller A, Wang RW, Schohl A, Fagotto F.
J Cell Biol. 2005 Aug 15;170(4):675-86.

Cell fate commitment/specification/determination
Plasticity!



Cell fate commitment/specification/determination

Plasticity!

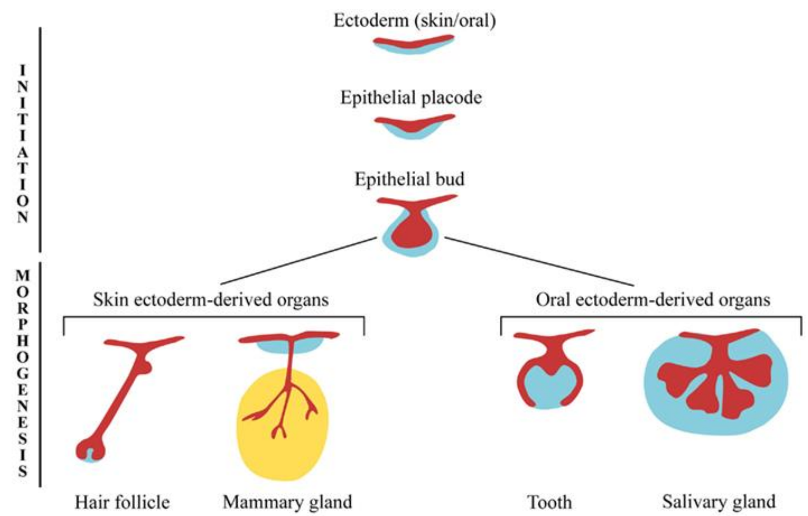


Figure 1. Ectodermal appendages during early stages of development. Ectoderm-derived structures start to develop from embryonic ectoderm upon mesenchymal inductive signals. The formation of the epithelial placodes, and their subsequent growth into the mesenchyme, is common to the early development of all ectodermal organs. At later developmental stages, epithelial buds undergo different morphogenetic programs resulting in the formation of highly specialized structures.

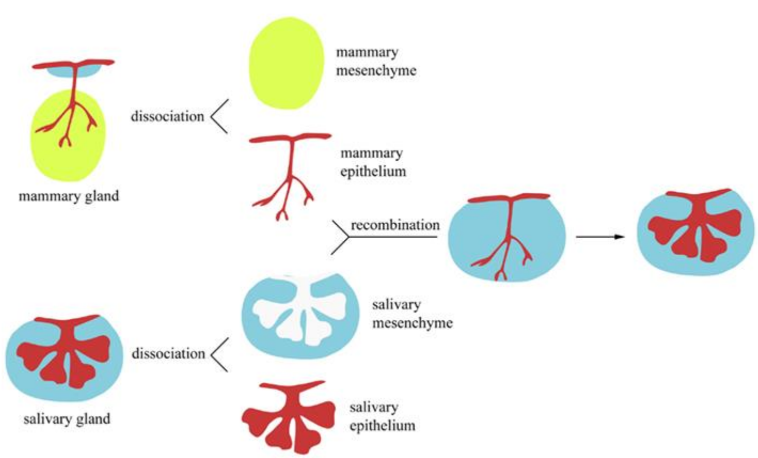


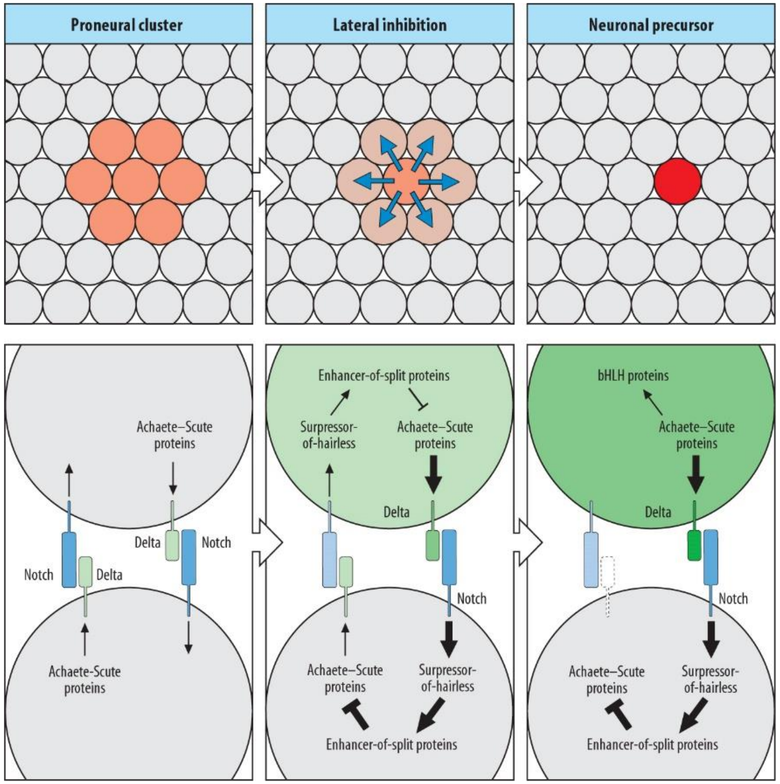
Figure 2. ***In vitro*** **heterotopic tissue recombination assay**. Epithelial and mesenchymal components from ectodermal appendages can be enzymatically and mechanically dissociated. Subsequently, they can be recombined with epithelium and mesenchyme from a different organ.

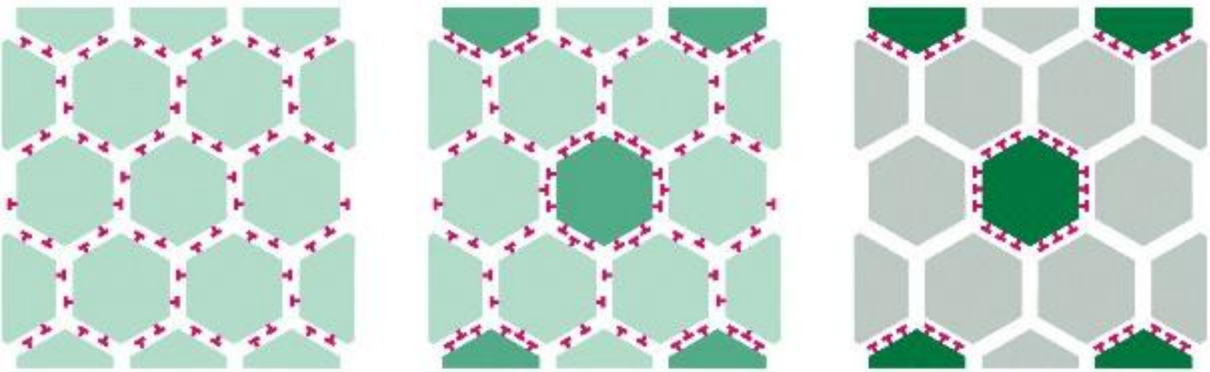
Front. Physiol., 25 April 2012

Introduction to cell fate and plasticity during embryonic development

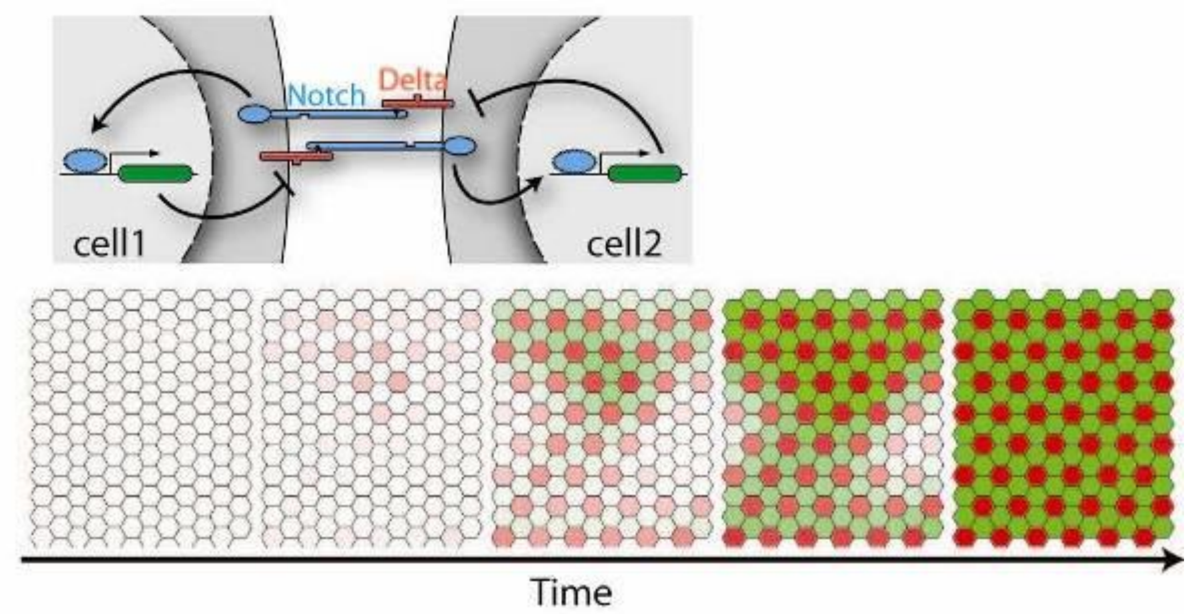
Introduction, fate maps, definitions
Cell determination = multistep process (ex: muscle)
Induction
Morphogens (ex: BMP)
Combinatorial control
Competence
Lateral inhibition
Asymmetric division/asymmetric distribution (germ cells)

Contact-mediated induction: lateral inhibition by the Notch pathway



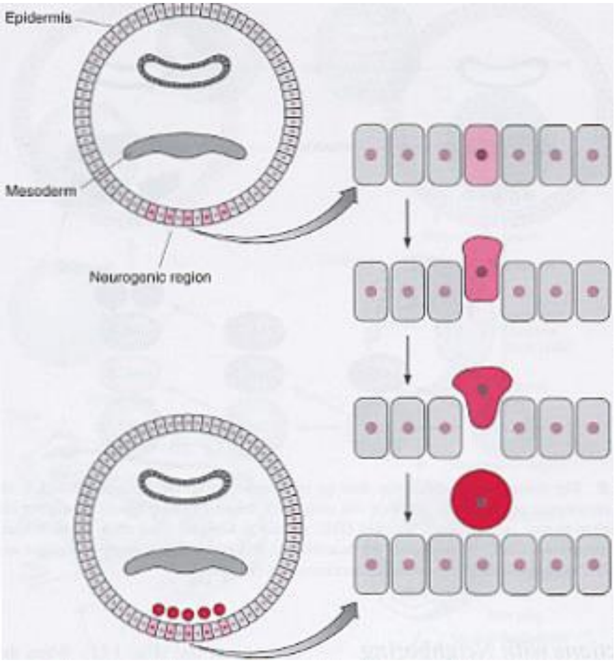


Contact-mediated induction: lateral inhibition by the Notch pathway

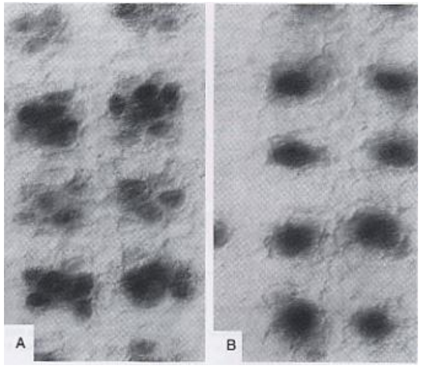


Contact-mediated induction: lateral inhibition by the Notch pathway

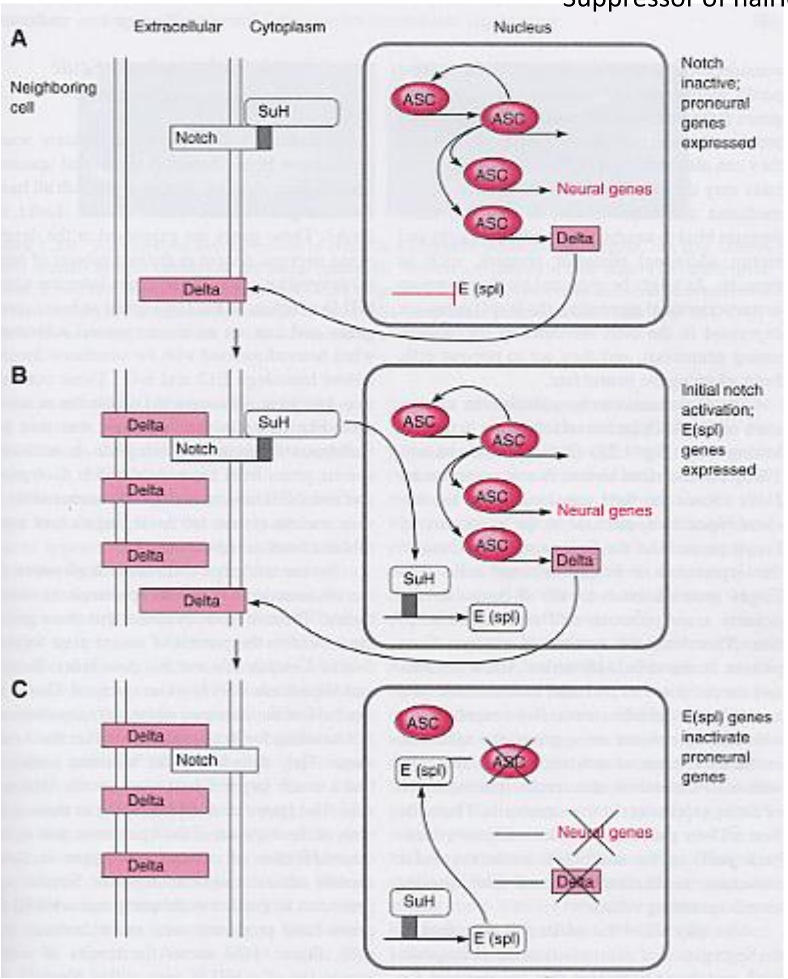
Formation of Drosophila Neuroblasts



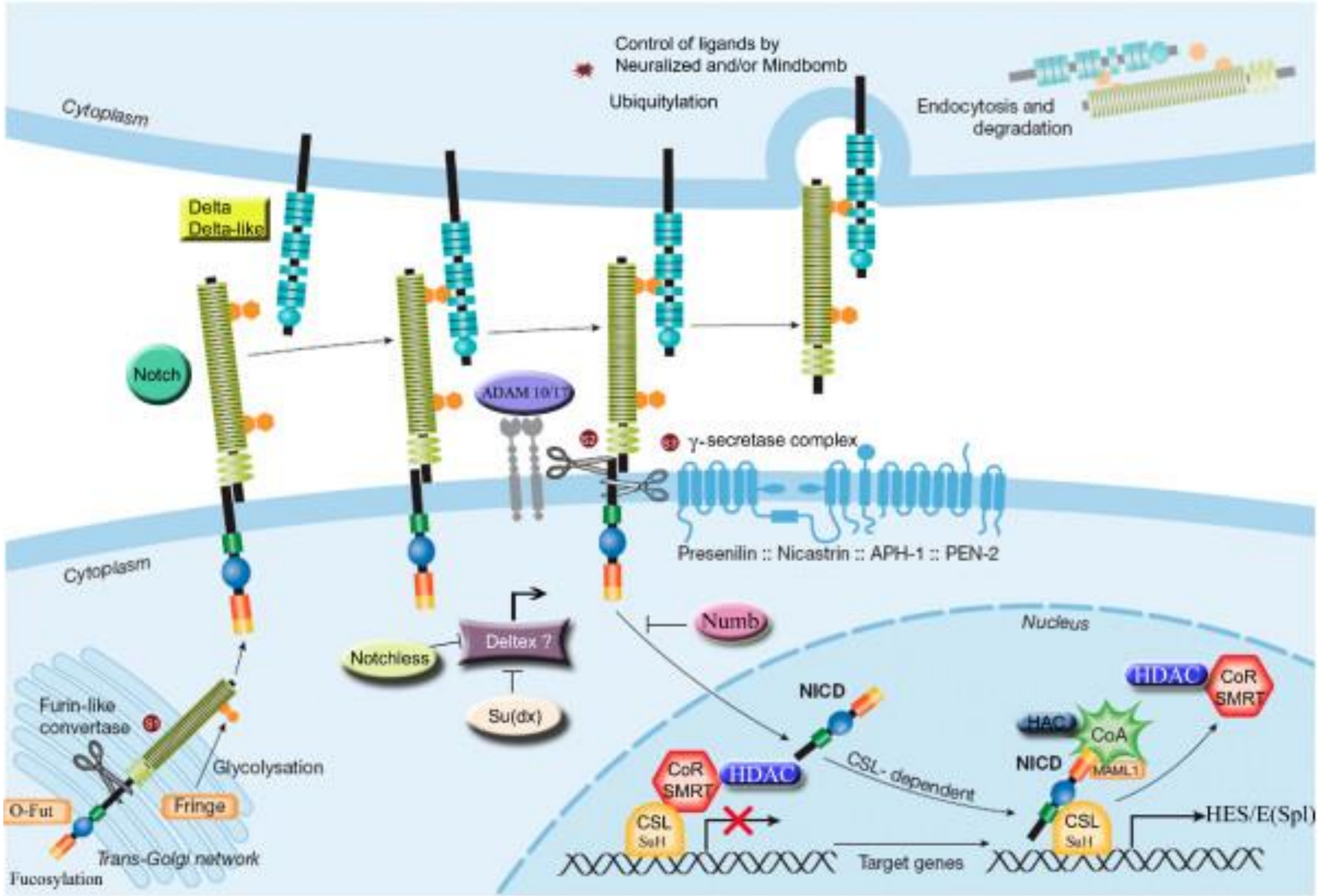
Drosophila Neuroblast Segregation



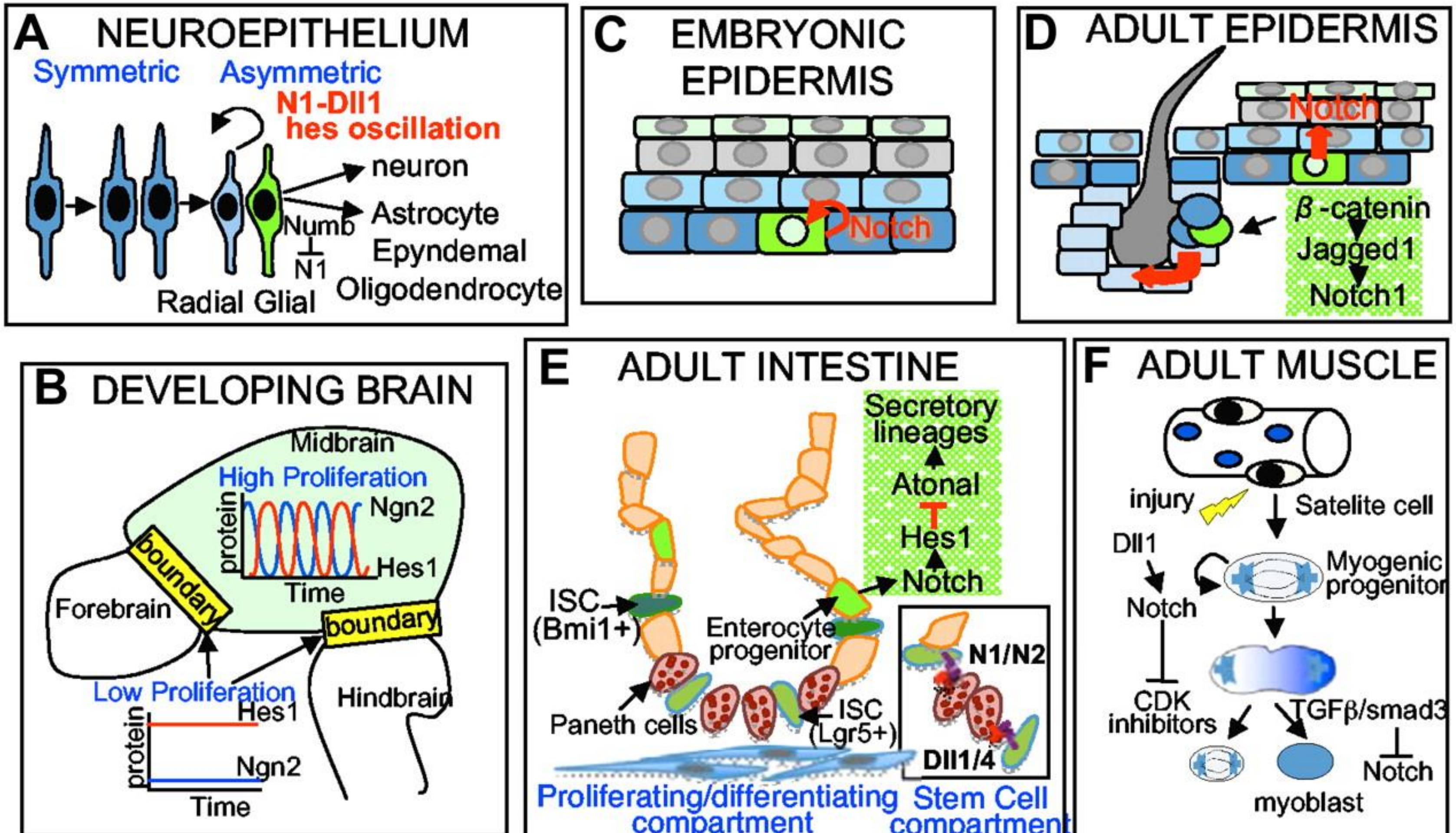
Achaete Scute
Enhancer of Split
Suppressor of hairless



Notch signaling



Examples of functions of Notch signaling (stem cell maintenance)



Anna Bigas and Lluis Espinosa
Blood 2012 119:3226-3235; doi:10.1182/blood-2011-10-355826

Introduction to cell fate and plasticity during embryonic development

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Cell determination = multistep process (ex: muscle)
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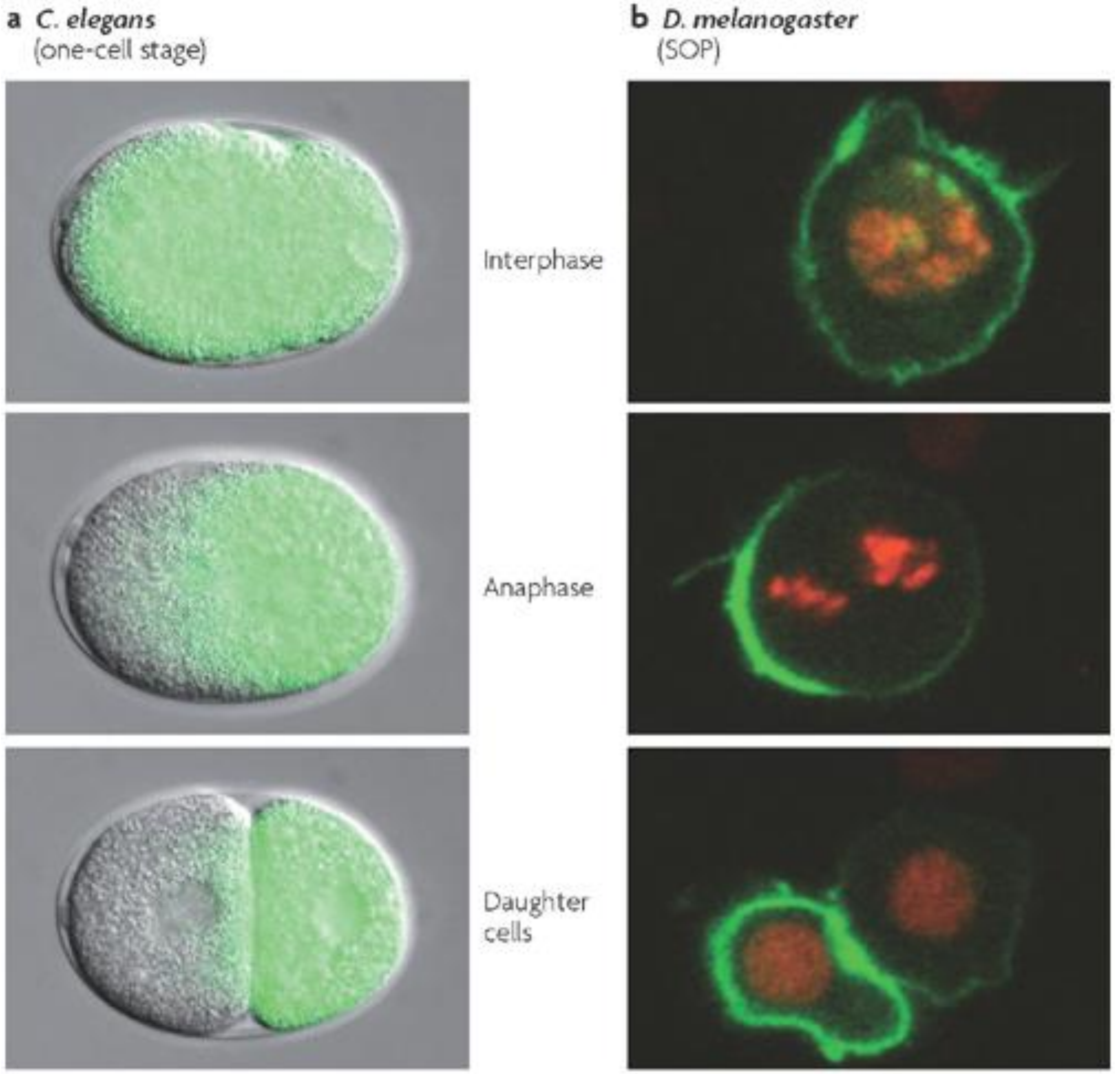
Creating asymmetry:
Asymmetric division
Asymmetric distribution of determinants

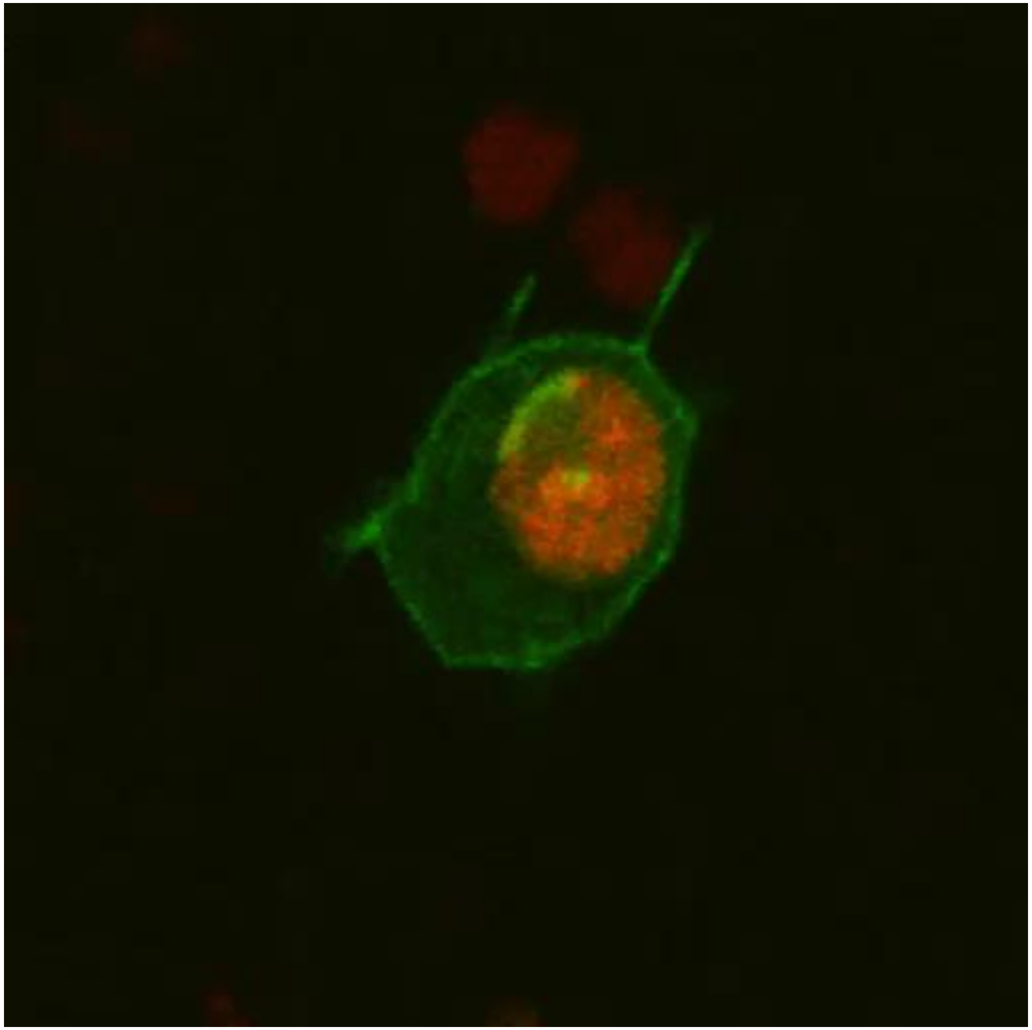


Nature Reviews | Molecular Cell Biology

Asymmetric division / asymmetric distribution of determinants

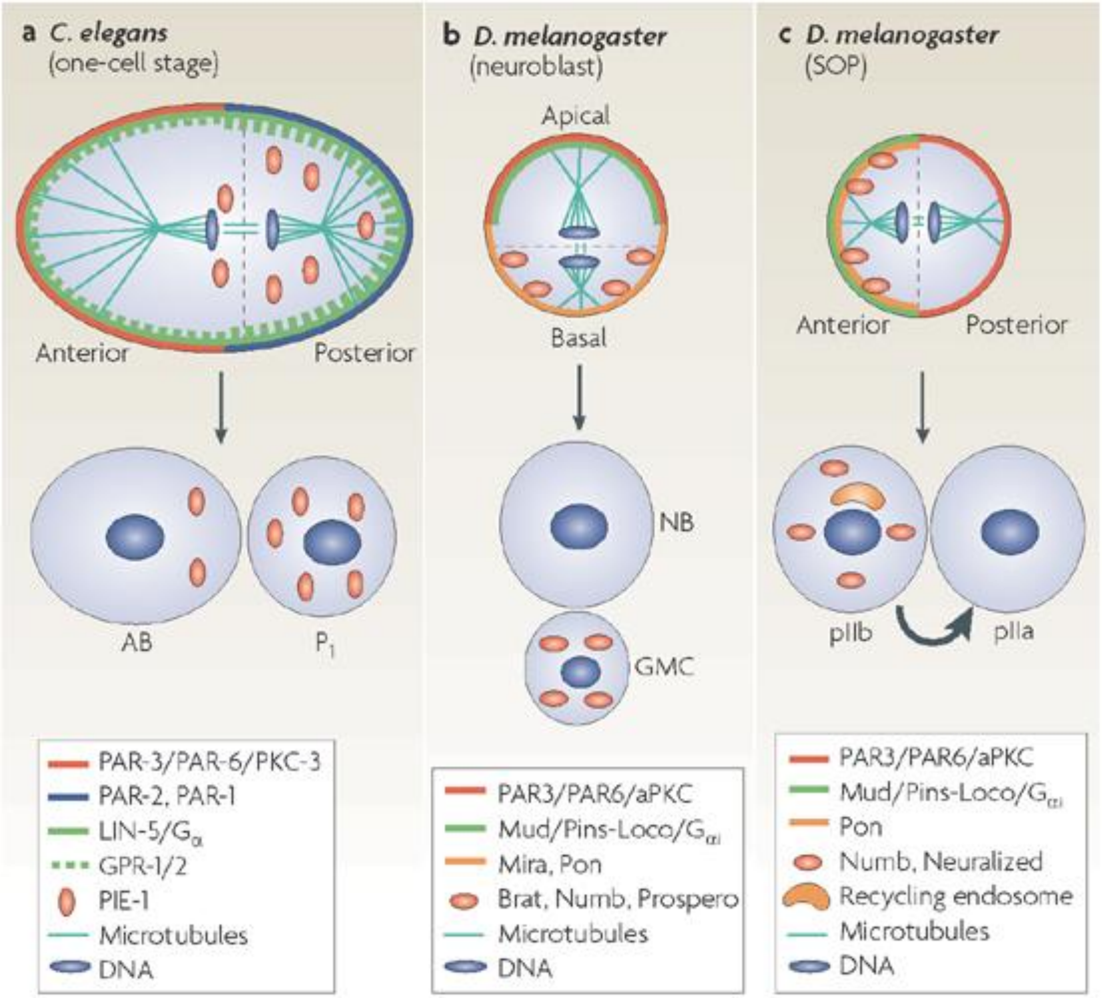
Polarization -> Segregation
+ Localized degradation

Asymmetric division / asymmetric distribution of determinants

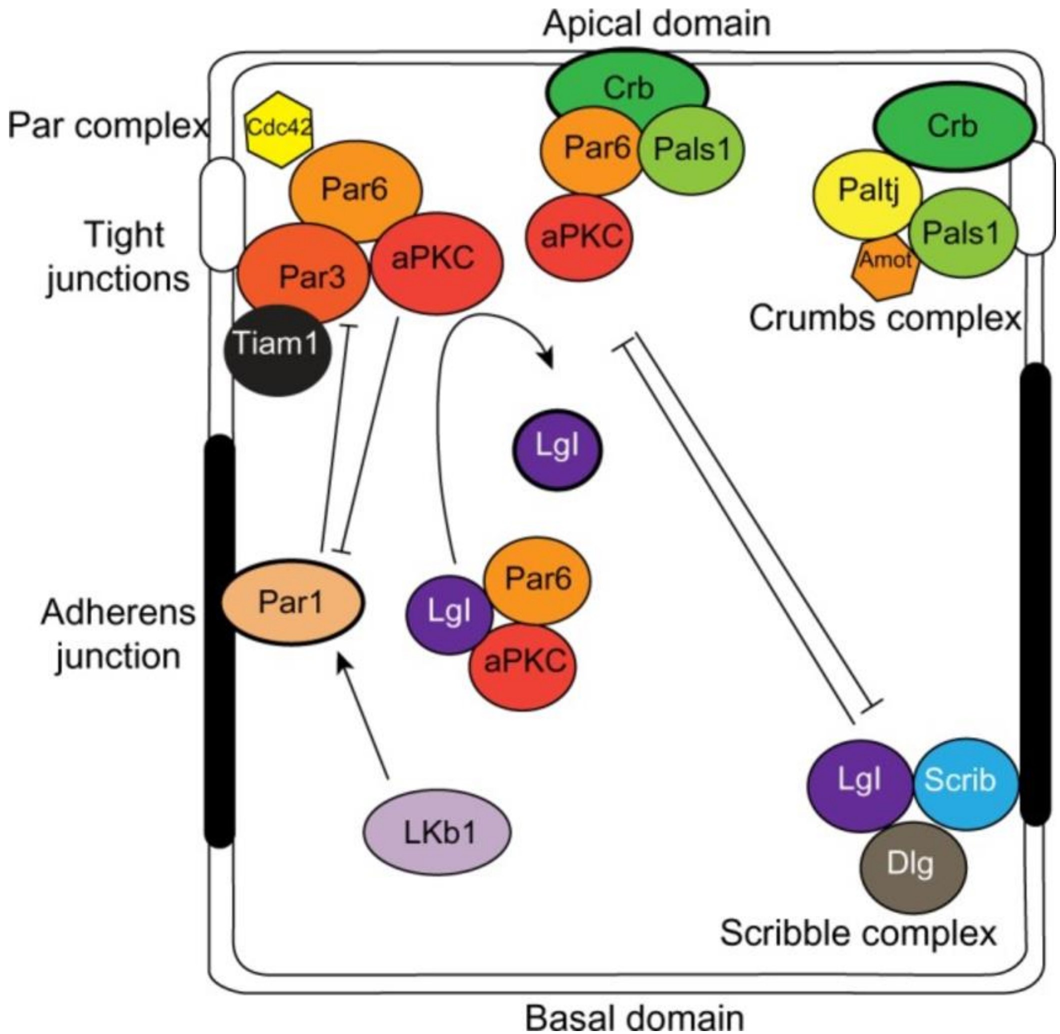


Asymmetric division / asymmetric distribution of determinants

Role of the
Par complexes

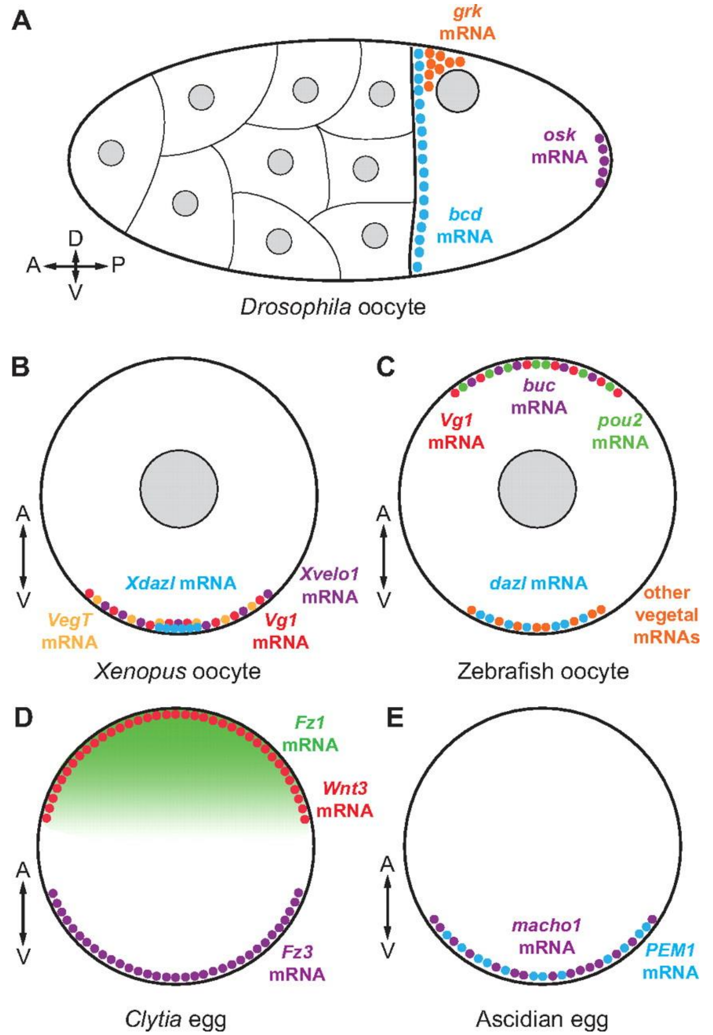


Nature Reviews | Molecular Cell Biology



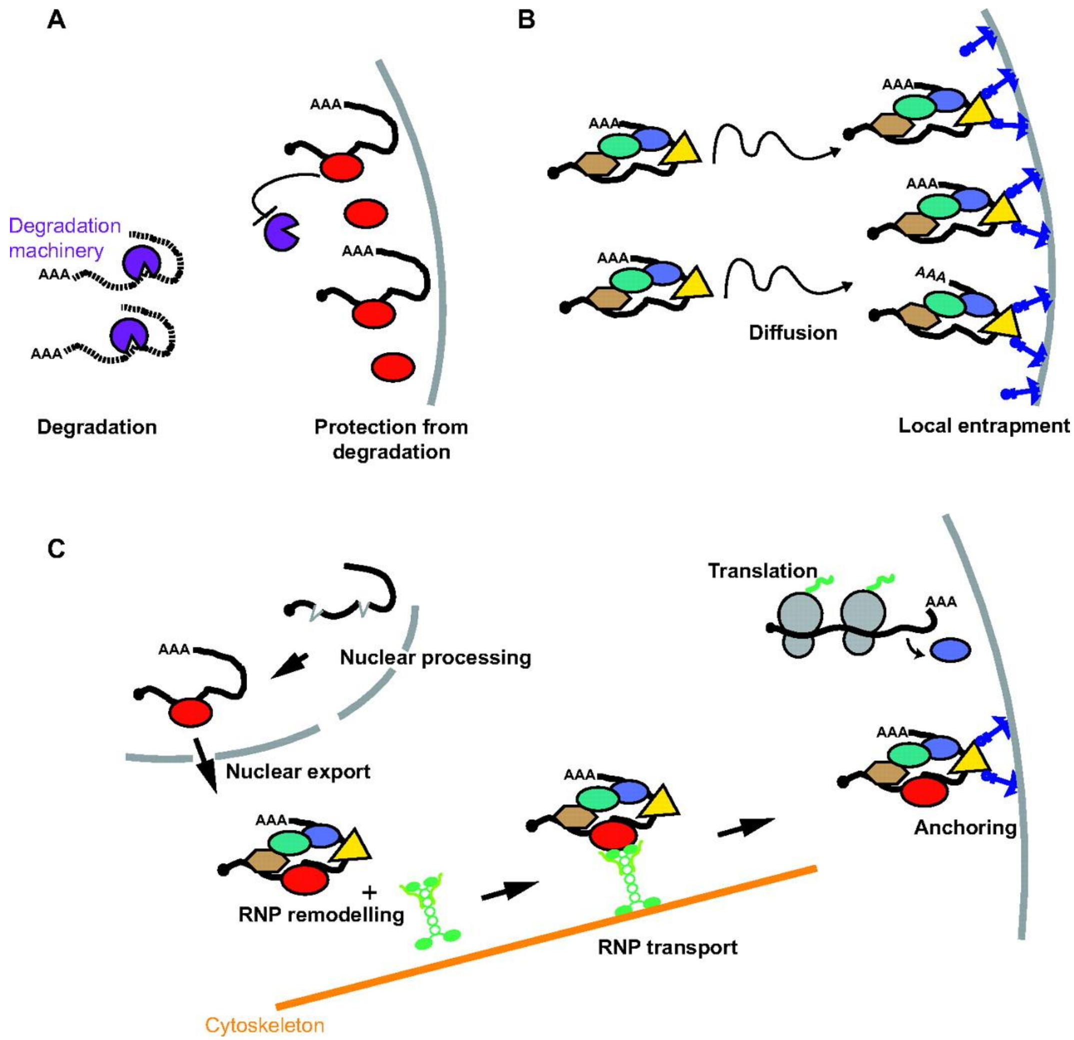
Apical–basal polarity is established and maintained by an evolutionarily conserved group of proteins that assemble into dynamic protein complexes (Figure 2).16–18 The Par complex consists of the multi-domain scaffolding protein, Par3, the adaptor Par6, atypical protein kinase C (aPKC), and the small GTPase cell division control protein 42 (Cdc42). Par3 binds directly with phospholipids at the plasma membrane and with the tight junction protein JAM-A19 and recruits Par6 and aPKC to the plasma membrane where Cdc42 induces a conformation change in Par6 that enables aPKC activation. The membrane localization of Par3, and subsequently Par6 and aPKC, is partly restricted by another Par protein, Par1b, which localizes to the basolateral domain. Par1b phosphorylates Par3, which creates a binding site for 14-3-3 proteins (also called Par5), and causes Par3 to dissociate from the cell cortex.20,21 In this way, basolateral Par1b excludes the Par complex from the basolateral domain and restricts it apically. Conversely, aPKC phosphorylates Par1b to exclude it from the apical membrane.22

Localized maternal mRNAs in eggs and oocytes.



Caroline Medioni et al. Development 2012;139:3263-3276

Three distinct mechanisms underlying mRNA localization.

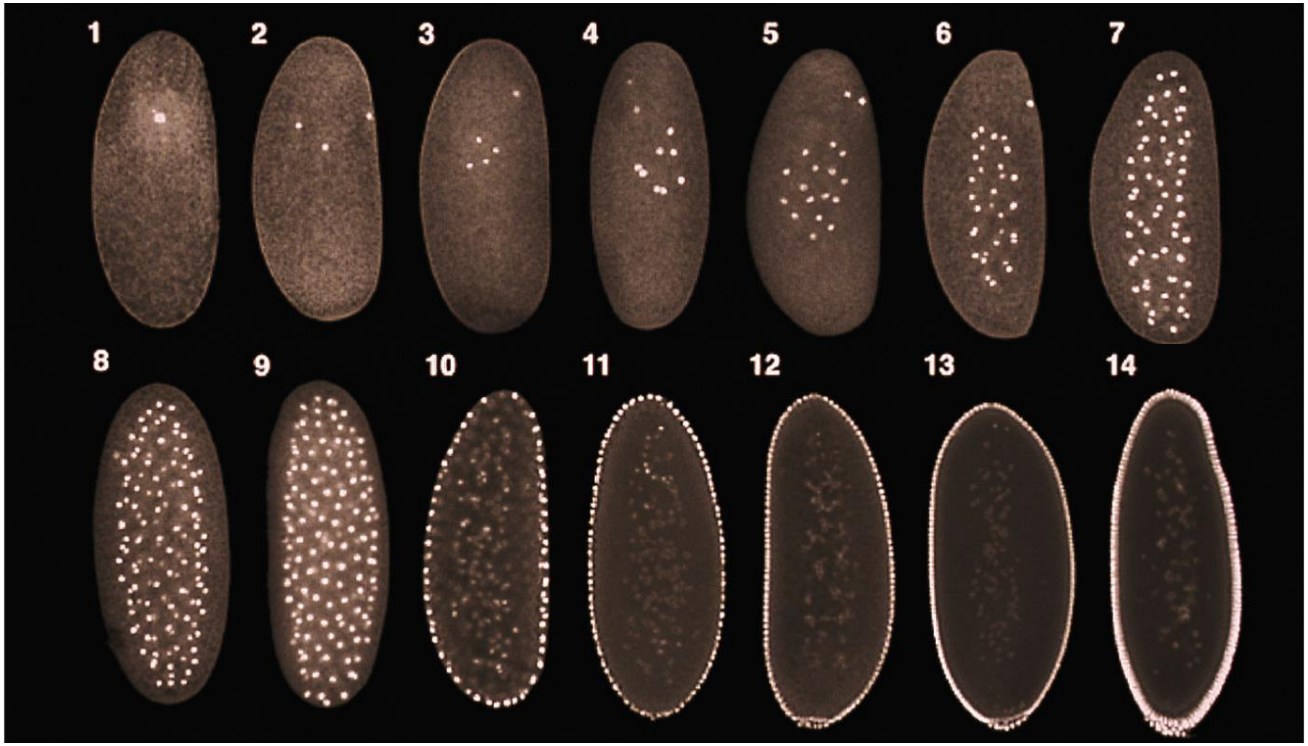


Caroline Medioni et al. Development 2012;139:3263-3276

Asymmetric division / asymmetric distribution of determinants

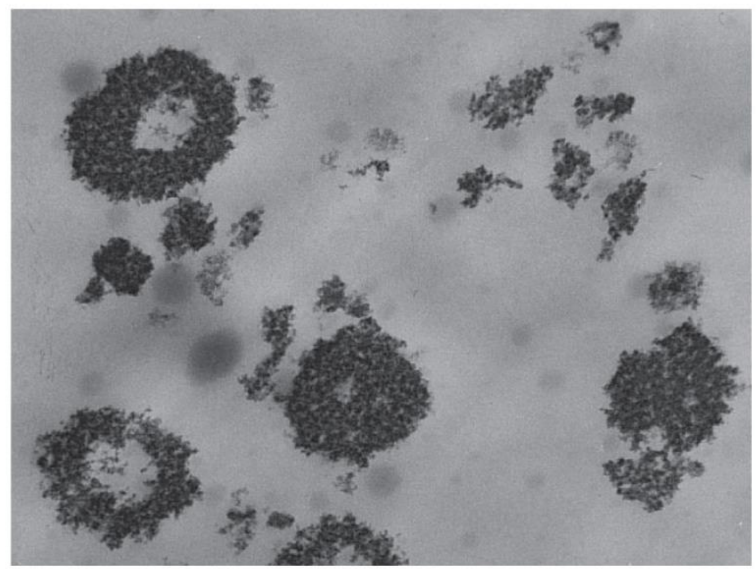
Germ cell determination and migration

***DEVELOPMENTAL BIOLOGY*, 9e, Figure 6.1**

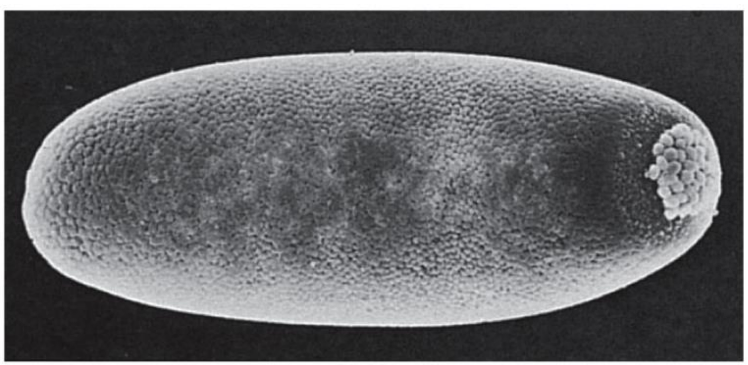


***DEVELOPMENTAL BIOLOGY*, 9e, Figure 16.3**

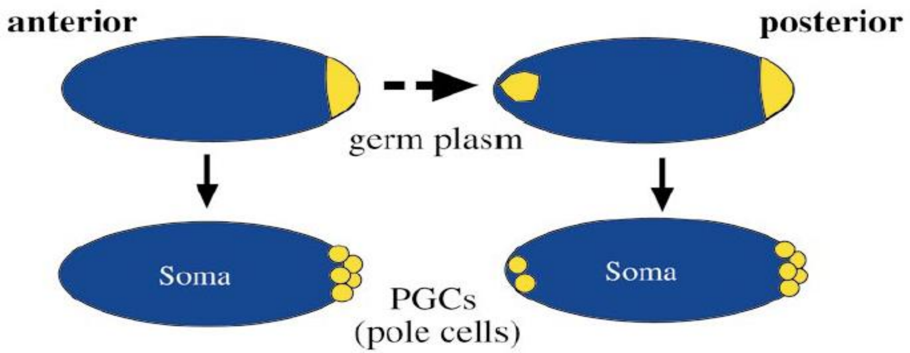
(A)



(B)



Polar granules



From Starz-Gaiano and Lehmann, Mech. Dev., 105, 5-18.

gene	protein
germ cell-less (gcl)	nuclear envelope protein; important for transcriptional quiescence
polar granule component (pgc)	peptide; important for transcriptional quiescence
vasa	RNA-binding protein
nanos	translation inhibitor; blocks somatic “fate”
tudor	novel; associated with mitochondria
oskar	recruits pole plasm components
piwi	argonaute protein, RNAi, gene silencing
aubergine	argonaute protein, RNAi, gene silencing

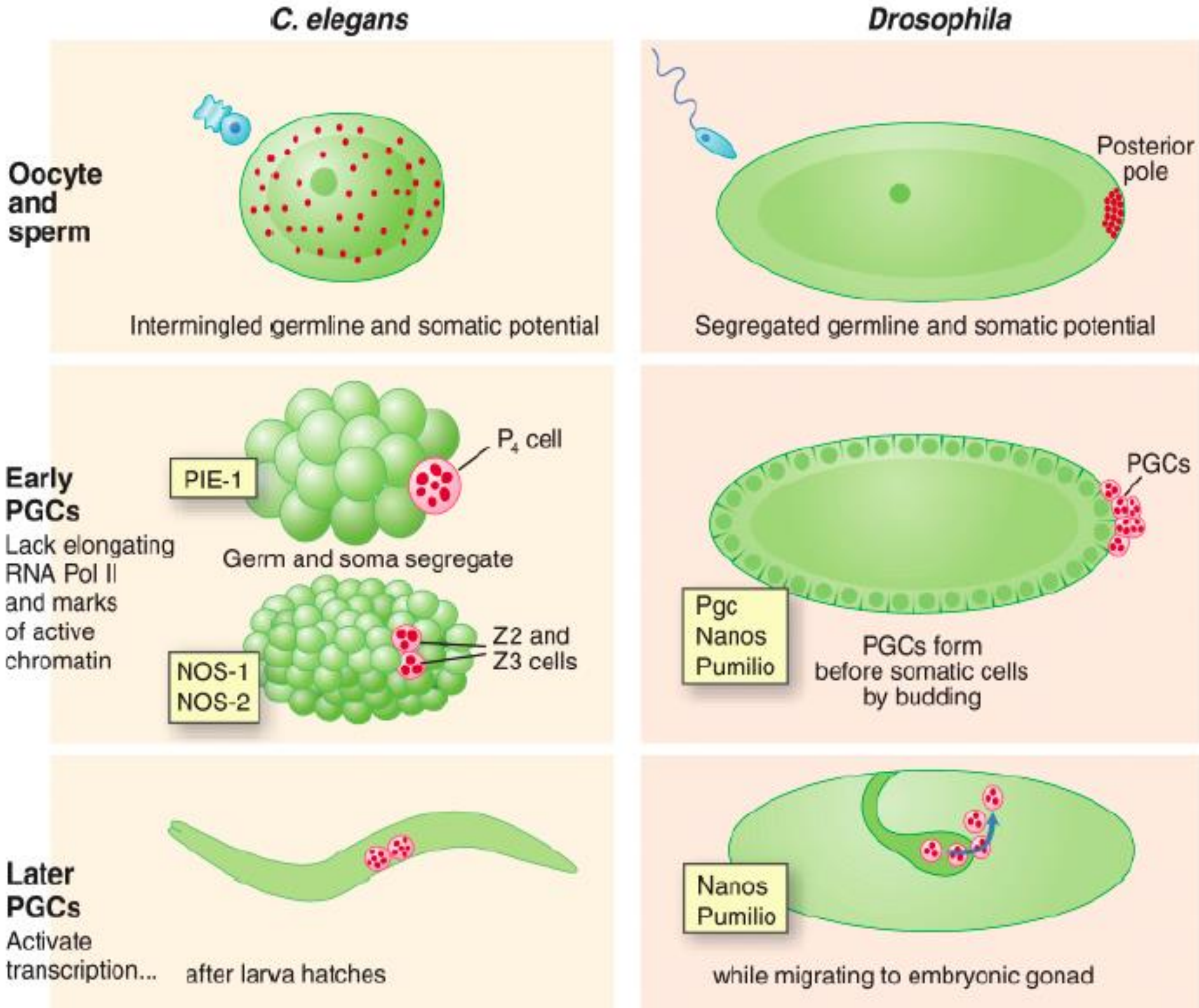
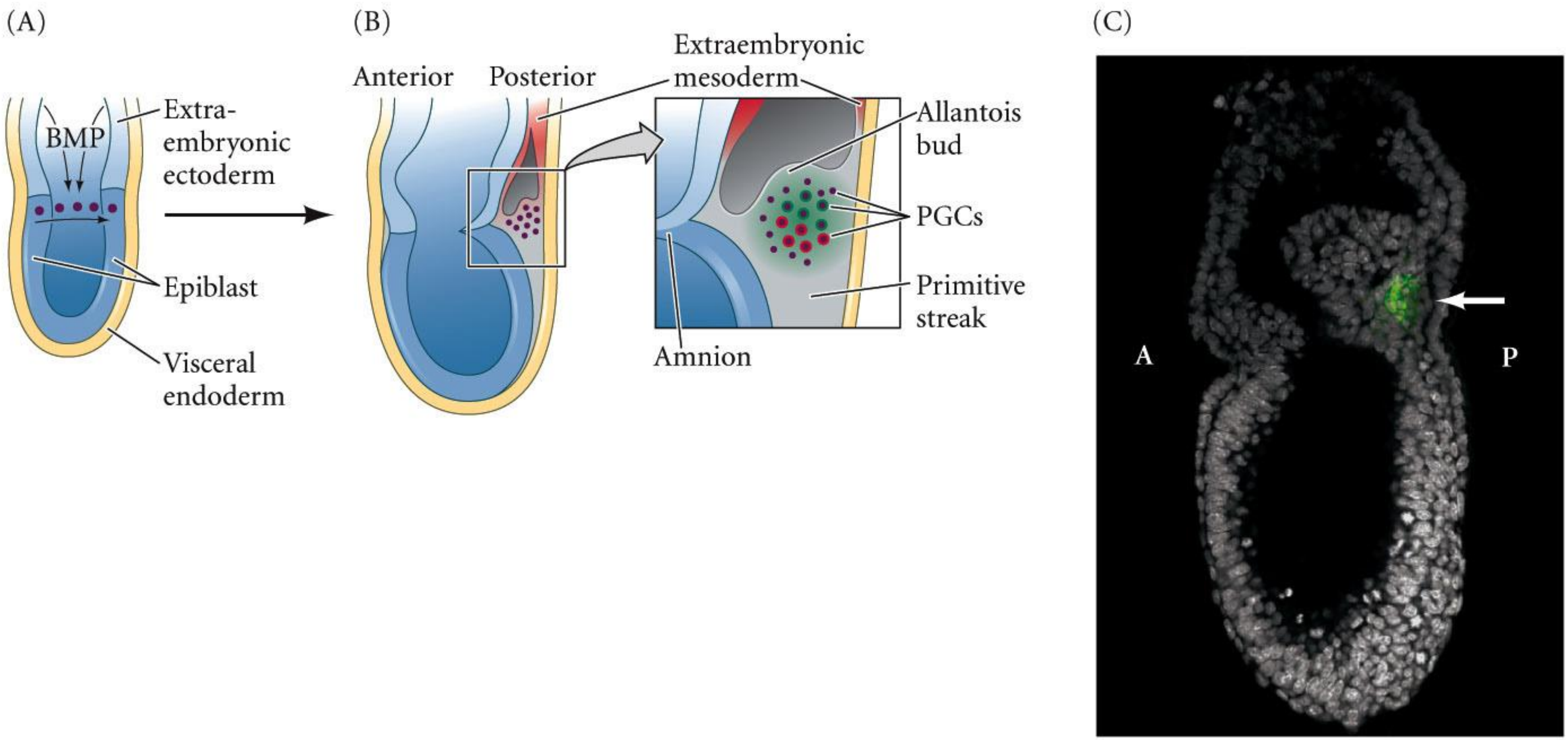


Fig. 1. Formation of PGCs and landmark stages in their development in *C. elegans* and *Drosophila*. Germ plasm is represented by red granules. Key regulators mentioned in the text are noted in yellow boxes. Blue arrow in final panel indicates direction of germ cell migration in *Drosophila*.

Strome and Lehmann (2007) Science 316, 392



DEVELOPMENTAL BIOLOGY, 9e, Figure 16.7

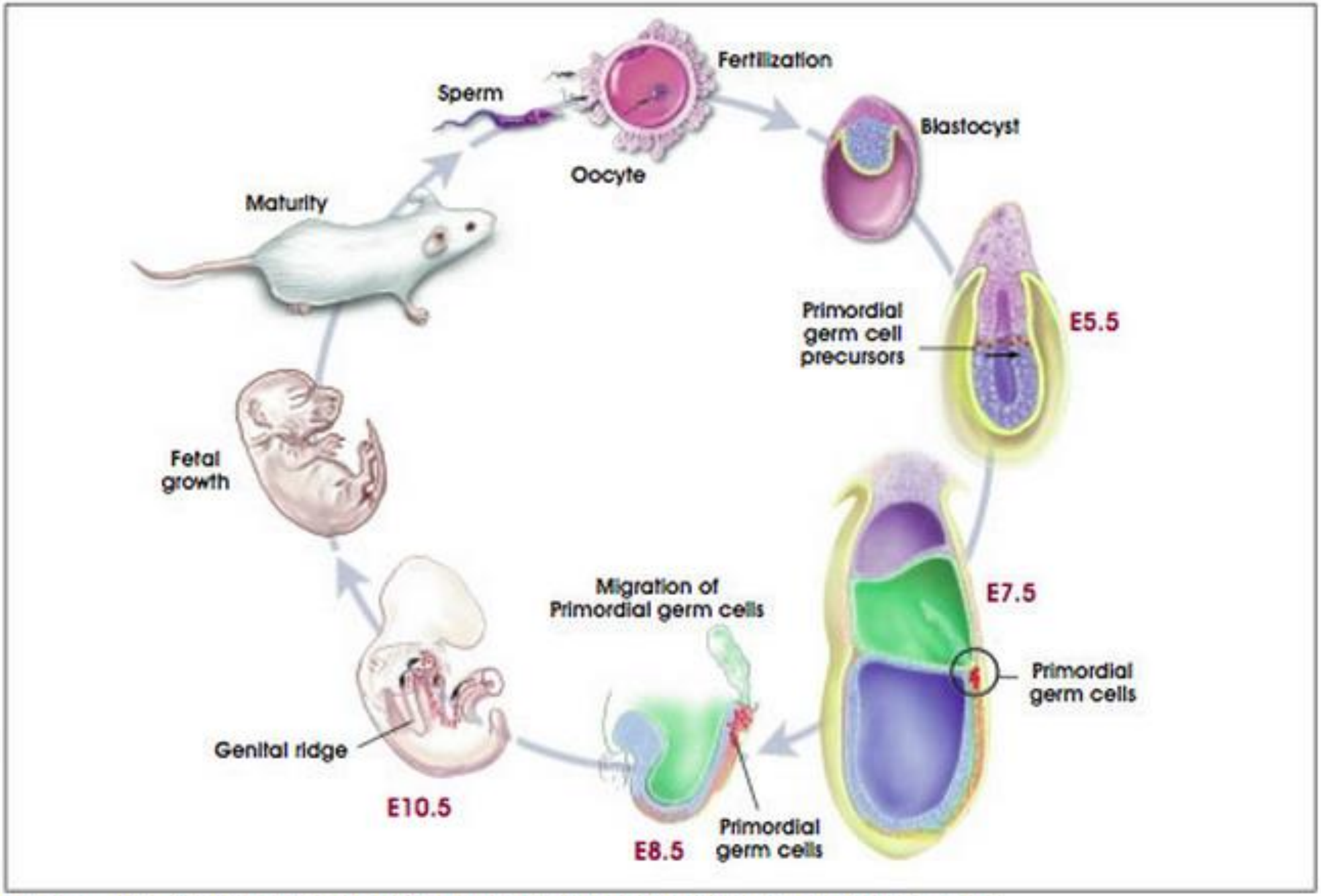
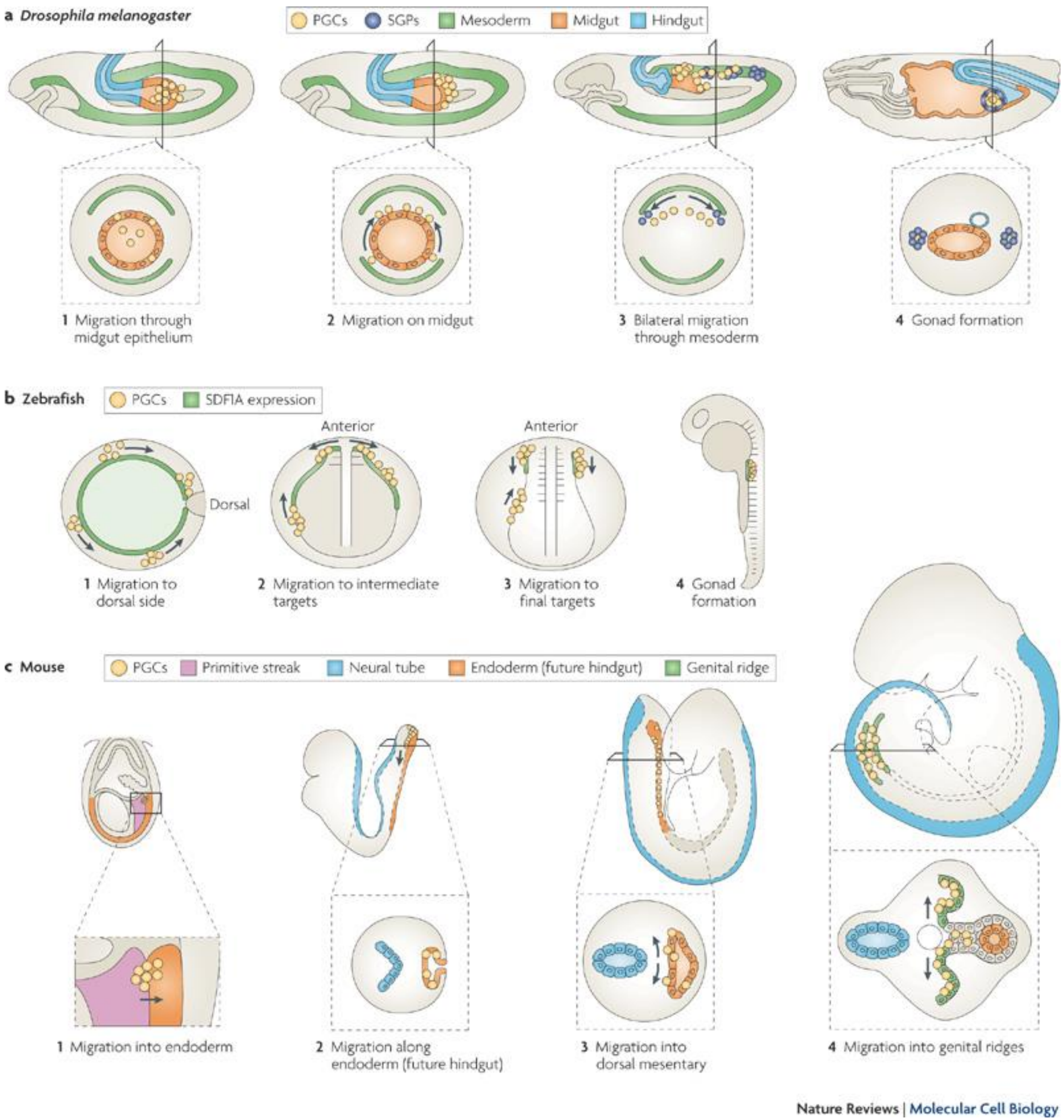


Figure A.5. Development of Mouse Embryonic Primordial Germ Cells.

http://www.youtube.com/watch?v=6td6ioz3WMM

http://www.youtube.com/watch?v=NXzWLLLe43o



Brian E Richardson, Ruth Lehmann Mechanisms guiding primordial germ cell migration: strategies from different organisms. Nat. Rev. Mol. Cell Biol.: 2010, 11(1);37-49